Additive effects of green tea and coffee on all-cause mortality in patients with type 2 diabetes mellitus: the Fukuoka Diabetes Registry

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ABSTRACT

Introduction The impact of consuming green tea or coffee on mortality in patients with diabetes is controversial. We prospectively investigated the impact of each beverage and their combination on mortality among Japanese patients with type 2 diabetes.

Research design and methods In all, 4923 patients (2790 men, 2133 women) with type 2 diabetes (mean age, 66 years) were followed prospectively (median, 5.3 years; follow-up rate, 99.5%). We evaluated the amount of green tea and coffee consumed using self-administered questionnaires.

Results During the follow-up period, 309 participants died. The consumption of green tea, coffee, and a combination of the beverages was associated with reduced all-cause mortality. Multivariable-adjusted hazard ratios (95% CIs) for green tea were as follows: none 1.0 (referent); 0.85 (0.60–1.22) for ≤1 cup/day; 0.73 (0.51–1.03) for 2–3 cups/day; 0.60 (0.42–0.85) for ≥4 cups/day; and P for trend, 0.002. For coffee, they were: none 1.0 (referent); 0.88 (0.66–1.18) for <1 cup/day; 0.81 (0.58–1.13) for 1 cup/day; 0.59 (0.42–0.82) for ≥2 cups/day; P for trend, 0.002. With the combination they were 1.0 (referent) for no consumption of green tea and coffee; 0.49 (0.24–0.99) for 2–3 cups/day of green tea with <2 cups/day of coffee; 0.42 (0.20–0.88) for ≥4 cups/day of green tea with 1 cup/day of coffee; and 0.37 (0.18–0.77) for ≥4 cups/day of green tea with ≥2 cups/day of coffee.

Conclusions Higher consumption of green tea and coffee was associated with reduced all-cause mortality: their combined effect appeared to be additive in patients with type 2 diabetes.

INTRODUCTION

Worldwide, the number of patients with diabetes is increasing in both developed and developing countries.1 Diabetic patients are at increased risk for classical micro- and macrovascular diseases as well as nonclassical diseases, such as dementia, malignancy, and fragility fracture, which affect both quality of life and life expectancy.2 Recent advances in therapeutics (such as sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, and bariatric surgery) have been remarkable, however, lifestyle improvements are still regarded as the basic therapy.3 Lifestyle management comprises physical activity, smoking cessation, and nutrition therapy (including both food and beverages).3 However, epidemiological research on nonalcoholic beverages, such as green tea and coffee, has been scarce for diabetic patients.

Asian, especially East Asian, populations have a traditional habit of drinking green tea. Green tea derives from fresh leaves of Camellia sinensis, and it contains various chemicals, such as phenolic compounds, theanine, and various flavonoids.4 Green tea has been reported to have many health benefits, such as reduced all-cause mortality.5 However, the impact of consuming green tea and coffee on the longevity of Japanese people with type 2 diabetes is controversial.6 We prospectively investigated the impact of green tea and coffee consumption on all-cause mortality in Japanese patients with type 2 diabetes.
and caffeine. Through antioxidant, anti-inflammatory, or anti-bacterial properties, higher green tea consumption has been reported to confer health benefits, including preventing such chronic diseases as diabetes mellitus, and reduce mortality. Hitherto, however, no studies have investigated the association between green tea consumption and mortality in diabetic patients.

Coffee is one of the most frequently consumed beverages worldwide. It contains numerous bioactive chemicals, including phenolic compounds and caffeine, that have been reported to impact health through various mechanisms, such as antioxidant, anti-inflammatory, and anti-mutagenic effects; the result is a reduced risk of developing type 2 diabetes, dyslipidemia, or malignancy. In contrast to these health-promoting effects, coffee also has harmful effects, such as increasing blood pressure and the risk of myocardial infarction. In the general population, there is growing evidence that coffee consumption is associated with reduced risk of all-cause and cause-specific mortality. However, few epidemiological studies have examined this association in diabetic patients, and the results are controversial. This discrepancy may be due to the presence of diabetic complications, including cardiovascular disease (CVD), which could be affected by caffeine consumption. Further, most studies have been conducted only with developed country populations, which have higher risks of CVD than Asian ones.

Recently, green tea has attracted considerable attention as a healthy beverage in developed countries. Japan has the culinary culture of both its own traditional food with green tea and developed country food with coffee: this provides a unique opportunity to investigate the combined effect of green tea and coffee consumption on mortality. Accordingly, in the present study, we prospectively investigated the impact of green tea, coffee consumption, and their combination on all-cause and cause-specific mortality in Japanese patients with type 2 diabetes.

**RESEARCH DESIGN AND METHODS**

**Study participants**

The Fukuoka Diabetes Registry is a multicenter prospective study (UMIN Clinical Trial Registry 000002627) designed to investigate the effect of modern treatments and lifestyles on the prognoses of patients with diabetes mellitus. The registry includes patients who regularly attended teaching hospitals certified by the Japan Diabetes Society or certified diabetes clinics in Fukuoka Prefecture, Japan. In all, 5131 patients with diabetes mellitus aged 20 years or older were registered during baseline registration as baseline. Laboratory measurements

Blood samples were collected by venipuncture, and spot urine samples were obtained. Hemoglobin A1c (HbA1c) was determined by high-performance liquid chromatography (Tosoh Corp., Tokyo.). Serum low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, creatinine, and urinary creatinine...
concentrations were measured using enzymatic methods.
We measured urinary albumin using an immunoneph-
elometry method (Medical and Biological Laboratories
Co., Ltd., Nagoya). We calculated estimated glomer-
ular filtration rates (eGFR) based on serum creatinine
using the equation proposed by the Japanese Society of
Nephrology. Urinary albumin-creatinine ratio (UACR)
levels were calculated by dividing the urinary albumin
values by the urinary creatinine concentrations.

Mortality follow-up
The primary outcome in this study was all-cause mortality.
Participants received an annual follow-up during their
survival through interviews, medical records, letters,
telephone calls, and municipal registration of resi-
dence. During the follow-up period (median, 5.3 years),
27 participants were lost to follow-up (follow-up rate,
99.5%). The underlying cause of death was determined
based on medical records or death certificates: it was
coded according to the International Classification of
Diseases, 10th revision.

Statistical analysis
The age- and sex-adjusted mortality rate was calculated
using the person-years method: we calculated mortality
in each 10-year age-group by sex and then weighted it
based on the distribution of all participants. The Cox
proportional-hazards models were used to estimate the
HRs and 95% CIs for mortality. In the multivariable-
adjusted model, we selected the following covariates,
known to be a potential risk or protective factors for
mortality: age, sex, BMI, diabetes duration, current
smoking habit, current alcohol intake, LTPA, sleep dura-
tion, HbA1c, UACR, systolic blood pressure, LDL choles-
terol, history of CVD, and cancer. We conducted further
adjustment for the coffee-drinking habit to analyze the
association between green tea and mortality, and vice
versa. We confirmed the proportional hazard assumption
graphically and using the Schoenfeld residual test: the
HRs remained significant after additional adjustments
for coffee consumption. Cause-specific mortality for
cancer was not associated with the amount of green tea
consumed: the association of the amount of green tea
consumed with CVD was marginally insignificant (P for
trend, 0.08). In the coffee groups, all-cause mortality was
also significantly reduced according to the amount of
coffee consumed (P for trend, 0.001). The multivariable-adjusted HR was significantly lower in participants who
consumed ≥4 cups/day of green tea compared with those who did not drink green tea (HR, 0.60; 95% CI, 0.42 to 0.85). Further, the
HR remained significant after additional adjustments
for coffee consumption. Cause-specific mortality for
cancer was not associated with the amount of coffee consumed: the association of the amount of green tea
consumed with CVD was marginally insignificant (P for
trend, 0.06).

Figure 1 shows the multivariable-adjusted HRs of all-
cause mortality according to combined green tea and
coffee consumption. When the mortality in participants
drinking neither green tea nor coffee was set as the
referred, multivariable-adjusted HRs were significantly
reduced as follows: in those consuming 2–3 cups of green
tea with ≥2 cups/day of coffee (HR, 0.49; 95% CI, 0.24
to 0.99); consuming ≥4 cups/day of green tea with 1
cup/day of coffee (HR, 0.42; 95% CI, 0.20 to 0.88); and
drinking ≥4 cups of green tea with ≥2 cups/day of coffee
(HR, 0.37; 95% CI, 0.18 to 0.77) (table 3).

RESULTS
Table 1 summarizes the baseline clinical characteristics
of the four groups divided according to the amount of
green tea or coffee consumed. With the green tea
groups, mean age, duration of diabetes, sleep duration,
HDL cholesterol, systolic blood pressure, and frequency
of cancer history increased in participants with higher
green tea consumption. By contrast, the proportion of
males, current smokers and current drinkers, eGFR,
and diastolic blood pressure decreased in participants
with higher green tea consumption. With the coffee
groups, mean age, sleep duration, UACR, systolic blood
pressure, frequency of taking antihypertensive or anti-
platelet drugs, history of CVD, and cancer decreased in
participants with higher coffee consumption. Conversely,
the proportion of males, current smokers and current
drinkers, mean LTPA, HbA1c, eGFR, LDL cholesterol,
HDL cholesterol, and diastolic blood pressure increased
in participants with higher coffee consumption.

During the follow-up period (median, 5.3 years;
follow-up rate, 99.5%), 309 participants (218 men, 91
women) died. The main causes of death were cancer
(n=114) and CVD (n=76). Table 2 presents the number
of all-cause and cause-specific deaths, crude incidence,
mortality. The underlying cause of death was determined
based on medical records or death certificates: it was
coded according to the International Classification of
Diseases, 10th revision.

Statistical analysis
The age- and sex-adjusted mortality rate was calculated
using the person-years method: we calculated mortality
in each 10-year age-group by sex and then weighted it
based on the distribution of all participants. The Cox
proportional-hazards models were used to estimate the
HRs and 95% CIs for mortality. In the multivariable-
adjusted model, we selected the following covariates,
known to be a potential risk or protective factors for
mortality: age, sex, BMI, diabetes duration, current
smoking habit, current alcohol intake, LTPA, sleep dura-
tion, HbA1c, UACR, systolic blood pressure, LDL choles-
terol, history of CVD, and cancer. We conducted further
adjustment for the coffee-drinking habit to analyze the
association between green tea and mortality, and vice
versa. We confirmed the proportional hazard assumption
graphically and using the Schoenfeld residual test: the
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consumed with CVD was marginally insignificant (P for
trend, 0.08). In the coffee groups, all-cause mortality was
also significantly reduced according to the amount of
coffee consumed (P for trend, 0.001). The multivariable-
adjusted HR was significantly lower in participants who
consumed ≥4 cups/day of coffee than in those who did
not consume coffee (HR, 0.59; 95% CI, 0.42 to 0.82).
That association remained significant after further
adjustments for green tea consumption. Cause-specific
mortality for cancer was not associated with the amount of
coffee consumed: the association of the amount of
coffee consumption with CVD was marginally insignifi-
cant (P for trend, 0.06).

Figure 1 shows the multivariable-adjusted HRs of all-
cause mortality according to combined green tea and
coffee consumption. When the mortality in participants
drinking neither green tea nor coffee was set as the
referred, multivariable-adjusted HRs were significantly
reduced as follows: in those consuming 2–3 cups of green
tea with ≥2 cups/day of coffee (HR, 0.49; 95% CI, 0.24
to 0.99); consuming ≥4 cups/day of green tea with 1
cup/day of coffee (HR, 0.42; 95% CI, 0.20 to 0.88); and
drinking ≥4 cups of green tea with ≥2 cups/day of coffee
(HR, 0.37; 95% CI, 0.18 to 0.77) (table 3).

CONCLUSIONS
In this prospective study, we found that higher green
tea and coffee consumption was significantly associated
with decreased all-cause mortality in patients with type
2 diabetes. This association remained significant after
adjusting for potential confounders: the impact of each
beverage on mortality was independent. Similar trends
were evident in analyses of CVD-specific mortality.
Further, the combination of higher green tea and coffee consumption significantly reduced all-cause mortality risk by 63%.

Hitherto, little research has investigated the association between green tea consumption and mortality in diabetic patients. Some epidemiological studies from Japan and China have reported the association between green tea consumption and mortality in the general population, including diabetic and non-diabetic individuals. The Ohsaki Study was the first large-scale investigation on this subject: among 40,530 Japanese men and women, it found that those who consumed ≥5 cups/day of green tea had a 15% lower risk of all-cause mortality than those drinking <1 cup/day. A meta-analysis of five cohort studies of the general population (including diabetic and non-diabetic individuals) demonstrated that the HRs (95% CIs) of the highest vs the lowest green tea consumption were 0.80 (0.68–0.93) for all-cause mortality and 0.67 (0.52–0.86) for cardiovascular disease mortality.

Table 1: Baseline clinical characteristics according to amount of green tea or coffee consumed among Japanese participants with type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>≤1 cup/d</th>
<th>2–3 cups/d</th>
<th>≥4 cups/d</th>
<th>None</th>
<th>&lt;1 cup/d</th>
<th>1 cup/d</th>
<th>≥2 cups/d</th>
</tr>
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<tbody>
<tr>
<td><strong>N</strong></td>
<td>607</td>
<td>1143</td>
<td>1389</td>
<td>1784</td>
<td>994</td>
<td>1306</td>
<td>963</td>
<td>1660</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>64.6±10.2</td>
<td>62.5±10.8</td>
<td>65.7±9.8</td>
<td>67.3±9.7</td>
<td>69.0±10.0</td>
<td>66.4±10.2</td>
<td>65.6±10.1</td>
<td>62.3±9.5</td>
</tr>
<tr>
<td><strong>Male sex (%)</strong></td>
<td>60.3</td>
<td>64.3</td>
<td>60.5</td>
<td>47.6</td>
<td>50.6</td>
<td>54.7</td>
<td>53.3</td>
<td>63.9</td>
</tr>
<tr>
<td><strong>Duration of diabetes (years)</strong></td>
<td>14.9±10.3</td>
<td>14.8±10.4</td>
<td>15.9±10.6</td>
<td>16.0±10.6</td>
<td>16.3±10.9</td>
<td>15.5±10.6</td>
<td>15.5±10.3</td>
<td>15.2±10.4</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>23.9±3.4</td>
<td>24.1±3.8</td>
<td>23.5±3.7</td>
<td>23.7±3.9</td>
<td>23.7±3.7</td>
<td>23.9±3.8</td>
<td>23.9±4.0</td>
<td>23.6±3.6</td>
</tr>
<tr>
<td><strong>Current smoker (%)</strong></td>
<td>24.9</td>
<td>20.7</td>
<td>18.85</td>
<td>15.1</td>
<td>12.6</td>
<td>12.1</td>
<td>15.1</td>
<td>29.2</td>
</tr>
<tr>
<td><strong>Current alcohol intake (%)</strong></td>
<td>40.5</td>
<td>45.7</td>
<td>42.6</td>
<td>31.8</td>
<td>30.5</td>
<td>38.8</td>
<td>40.9</td>
<td>43.5</td>
</tr>
<tr>
<td><strong>Depressive symptoms (%)</strong></td>
<td>10.2</td>
<td>9.6</td>
<td>7.5</td>
<td>8.7</td>
<td>9.7</td>
<td>9.3</td>
<td>7.5</td>
<td>8.6</td>
</tr>
<tr>
<td><strong>LTPA (MET h/week)</strong></td>
<td>12.3±16.1</td>
<td>11.2±14.7</td>
<td>11.5±14.0</td>
<td>12.0±15.3</td>
<td>11.3±14.8</td>
<td>11.3±14.9</td>
<td>12.5±15.2</td>
<td>11.8±14.8</td>
</tr>
<tr>
<td><strong>Sleep duration (h/day)</strong></td>
<td>6.8±1.4</td>
<td>6.7±1.3</td>
<td>6.9±1.3</td>
<td>6.9±1.5</td>
<td>7.0±1.6</td>
<td>6.9±1.4</td>
<td>6.9±1.3</td>
<td>6.7±1.3</td>
</tr>
<tr>
<td><strong>HbA₁c (%)</strong></td>
<td>7.4±1.0</td>
<td>7.4±1.0</td>
<td>7.4±1.0</td>
<td>7.5±1.1</td>
<td>7.4±1.1</td>
<td>7.4±1.0</td>
<td>7.4±1.0</td>
<td>7.5±1.1</td>
</tr>
<tr>
<td><strong>HbA₁c (mmol/mol)</strong></td>
<td>57.3±10.8</td>
<td>57.4±11.2</td>
<td>57.4±10.7</td>
<td>58.4±12.2</td>
<td>57.4±11.8</td>
<td>57.1±11.2</td>
<td>57.8±11.0</td>
<td>58.5±11.6</td>
</tr>
<tr>
<td><strong>eGFR (ml/min/1.73 m²)</strong></td>
<td>73.3±23.7</td>
<td>78.6±21.8</td>
<td>74.2±21.4</td>
<td>73.5±20.9</td>
<td>69.7±23.1</td>
<td>73.5±21.0</td>
<td>75.5±22.2</td>
<td>78.6±20.4</td>
</tr>
<tr>
<td><strong>UACR (mg/g Cr)</strong></td>
<td>246±780</td>
<td>175±690</td>
<td>178±583</td>
<td>195±620</td>
<td>251±771</td>
<td>209±666</td>
<td>189±695</td>
<td>145±509</td>
</tr>
<tr>
<td><strong>LDL cholesterol (mmol/l)</strong></td>
<td>2.9±0.7</td>
<td>2.8±0.7</td>
<td>2.9±0.7</td>
<td>2.9±0.7</td>
<td>2.8±0.7</td>
<td>2.8±0.7</td>
<td>2.8±0.7</td>
<td>2.9±0.7</td>
</tr>
<tr>
<td><strong>HDL cholesterol (mmol/l)</strong></td>
<td>1.4±0.4</td>
<td>1.5±0.4</td>
<td>1.5±0.4</td>
<td>1.5±0.4</td>
<td>1.4±0.4</td>
<td>1.4±0.4</td>
<td>1.5±0.4</td>
<td>1.5±0.4</td>
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<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td>130±18</td>
<td>130±17</td>
<td>130±17</td>
<td>132±17</td>
<td>131±18</td>
<td>132±17</td>
<td>131±17</td>
<td>129±16</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mmHg)</strong></td>
<td>75±11</td>
<td>75±11</td>
<td>75±11</td>
<td>74±11</td>
<td>73±11</td>
<td>74±11</td>
<td>75±11</td>
<td>75±10</td>
</tr>
<tr>
<td><strong>History of CVD (%)</strong></td>
<td>24.2</td>
<td>22.1</td>
<td>20.7</td>
<td>21.4</td>
<td>25.7</td>
<td>22.8</td>
<td>20.9</td>
<td>18.9</td>
</tr>
<tr>
<td><strong>History of cancer (%)</strong></td>
<td>7.1</td>
<td>8.5</td>
<td>9.4</td>
<td>10.7</td>
<td>11.1</td>
<td>9.4</td>
<td>10.4</td>
<td>7.7</td>
</tr>
<tr>
<td><strong>Insulin therapy (%)</strong></td>
<td>32.8</td>
<td>27.7</td>
<td>27.0</td>
<td>29.6</td>
<td>30.4</td>
<td>24.9</td>
<td>28.7</td>
<td>31.1</td>
</tr>
<tr>
<td><strong>Oral hypoglycemic agent (%)</strong></td>
<td>59.6</td>
<td>64.2</td>
<td>65.5</td>
<td>62.3</td>
<td>61.2</td>
<td>64.9</td>
<td>64.1</td>
<td>62.9</td>
</tr>
<tr>
<td><strong>Antihypertensive drugs (%)</strong></td>
<td>55.7</td>
<td>51.6</td>
<td>54.6</td>
<td>54.4</td>
<td>61.9</td>
<td>57.4</td>
<td>56.5</td>
<td>45.1</td>
</tr>
<tr>
<td><strong>Antiplatelet drugs (%)</strong></td>
<td>28.2</td>
<td>22.9</td>
<td>24.1</td>
<td>25.8</td>
<td>29.4</td>
<td>26.9</td>
<td>25.2</td>
<td>20.6</td>
</tr>
<tr>
<td><strong>Statin (%)</strong></td>
<td>43.0</td>
<td>44.4</td>
<td>41.0</td>
<td>44.7</td>
<td>43.9</td>
<td>40.8</td>
<td>48.4</td>
<td>42.3</td>
</tr>
<tr>
<td><strong>Coffee drinker (&gt;0 cup/d, %)</strong></td>
<td>75.1</td>
<td>87.0</td>
<td>81.5</td>
<td>75.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Green tea drinker (&gt;0 cup/d, %)</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>84.8</td>
<td>89.6</td>
<td>88.5</td>
<td>87.4</td>
</tr>
</tbody>
</table>

Values are expressed as means±SD or percentages.
BMI, body mass index; Cr, creatinine; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rates; HbA₁c, hemoglobin A₁c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LTPA, leisure-time physical activity; MET, metabolic equivalent; UACR, urinary albumin creatinine ratio.
Table 2  All-cause and cause-specific mortality according to amount of green tea or coffee consumed among Japanese participants with type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>Green tea consumption</th>
<th></th>
<th></th>
<th>Coffee consumption</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>≤1 cup/d</td>
<td>2–3 cups/d</td>
<td>≥4 cups/d</td>
<td>None</td>
<td>&lt;1 cup/d</td>
</tr>
<tr>
<td></td>
<td>(n=607)</td>
<td>(n=1143)</td>
<td>(n=1384)</td>
<td>(n=1784)</td>
<td>(n=994)</td>
<td>(n=1306)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(n=994)</td>
<td>(n=1660)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of death</td>
<td>50</td>
<td>74</td>
<td>87</td>
<td>98</td>
<td>94</td>
<td>91</td>
</tr>
<tr>
<td>Incidence (/1000PYs)</td>
<td>15.8</td>
<td>12.3</td>
<td>11.9</td>
<td>10.4</td>
<td>18.2</td>
<td>13.2</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.0 (ref.)</td>
<td>0.87 (0.61–1.24)</td>
<td>0.71 (0.50–1.00)</td>
<td>0.60 (0.43–0.85)</td>
<td>0.001</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Multivariable-adjusted</td>
<td>1.0 (ref.)</td>
<td>0.85 (0.60–1.22)</td>
<td>0.73 (0.51–1.03)</td>
<td>0.60 (0.42–0.85)</td>
<td>0.002</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>+Coffee</td>
<td>1.0 (ref.)</td>
<td>0.88 (0.61–1.26)</td>
<td>0.73 (0.51–1.03)</td>
<td>0.60 (0.42–0.85)</td>
<td>0.001</td>
<td>–</td>
</tr>
<tr>
<td>+Green tea</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.0 (ref.)</td>
<td>0.88 (0.66–1.18)</td>
</tr>
<tr>
<td>Cancer mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of death</td>
<td>16</td>
<td>26</td>
<td>39</td>
<td>33</td>
<td>32</td>
<td>33</td>
</tr>
<tr>
<td>Incidence (/1000PYs)</td>
<td>5.1</td>
<td>4.3</td>
<td>5.4</td>
<td>3.5</td>
<td>6.2</td>
<td>4.8</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.0 (ref.)</td>
<td>0.96 (0.52–1.80)</td>
<td>0.98 (0.55–1.76)</td>
<td>0.63 (0.34–1.15)</td>
<td>0.09</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Multivariable-adjusted</td>
<td>1.0 (ref.)</td>
<td>0.96 (0.52–1.80)</td>
<td>1.02 (0.57–1.83)</td>
<td>0.65 (0.35–1.19)</td>
<td>0.12</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>+Coffee</td>
<td>1.0 (ref.)</td>
<td>0.98 (0.53–1.84)</td>
<td>1.02 (0.57–1.84)</td>
<td>0.65 (0.35–1.19)</td>
<td>0.11</td>
<td>–</td>
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<tr>
<td>+Green tea</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.0 (ref.)</td>
<td>0.92 (0.56–1.50)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of deaths</td>
<td>13</td>
<td>22</td>
<td>15</td>
<td>26</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Incidence (/1000PYs)</td>
<td>4.1</td>
<td>3.7</td>
<td>2.1</td>
<td>2.8</td>
<td>4.5</td>
<td>3.3</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.0 (ref.)</td>
<td>0.97 (0.49–1.93)</td>
<td>0.47 (0.23–1.00)</td>
<td>0.62 (0.32–1.22)</td>
<td>0.06</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Multivariable-adjusted</td>
<td>1.0 (ref.)</td>
<td>1.03 (0.51–2.05)</td>
<td>0.53 (0.25–1.13)</td>
<td>0.66 (0.33–1.31)</td>
<td>0.09</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>+Coffee</td>
<td>1.0 (ref.)</td>
<td>1.06 (0.53–2.12)</td>
<td>0.54 (0.25–1.14)</td>
<td>0.65 (0.33–1.29)</td>
<td>0.08</td>
<td>–</td>
</tr>
<tr>
<td>+Green tea</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1.0 (ref.)</td>
<td>0.92 (0.51–1.64)</td>
</tr>
</tbody>
</table>

Multivariate adjustments included age, sex, BMI, diabetes duration, current smoking habit, current alcohol intake, LTPA, sleep duration, HbA1c, UACR, systolic blood pressure, LDL cholesterol, history of CVD and cancer. BMI, body mass index; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; LTPA, leisure-time physical activity; UACR, urinary albumin creatinine ratio.
The results of the present study are consistent with those of previous studies of the general population (including diabetic and non-diabetic individuals): however, we found the impact of green tea consumption to be even greater (HR for the highest vs lowest consumption, 0.60). To our knowledge, this is the first study to identify an association between higher green tea consumption and decreased all-cause mortality in type 2 diabetes patients.

The association between coffee consumption and mortality has been controversial in diabetic patients, although most studies have described beneficial effects in general populations (including diabetic and non-diabetic individuals). This association with diabetic patients was initially investigated with a Finnish diabetic population (3837 individuals) in 2006: a 30% significant reduction in all-cause mortality was observed in those who consumed ≥7 cups/day of coffee compared with those drinking 0–2 cups/day.16 However, the Health Professionals Follow-up Study of 3497 male diabetic patients found no association between coffee consumption and all-cause or CVD mortality.17 The National Health and Nutrition Examination Survey recently found that ≥200 mg/day of caffeine from coffee reduced all-cause mortality among 1974 women with diabetes, but not among men.19 Some large-scale studies of general populations have attempted to identify associations in subgroup analyses of diabetic patients. The National Institutes of Health-American Association of Retired Persons Diet and Health Study (total n=246,433) found that consuming ≥4 cups/day of coffee was associated with a 19% significant reduction of all-cause mortality in men and 14% insignificant reduction in women with self-reported diabetes.12 Similarly, in a US prospective cohort with 90,317 participants, drinking ≥4 cups/day of coffee was significantly associated with reduced all-cause mortality in diabetic patients.13

### Table 3

Multivariate-adjusted HR and 95% CIs of green tea and coffee consumption for all-cause mortality in patients with type 2 diabetes

<table>
<thead>
<tr>
<th>Green tea consumption</th>
<th>Coffee consumption</th>
<th>No</th>
<th>&lt;1 cup/d</th>
<th>1 cup/d</th>
<th>≥2 cups/d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event no. /at risk</td>
<td>14/151</td>
<td>13/136</td>
<td>11/111</td>
<td>12/209</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>1.0 (ref.)</td>
<td>0.95 (0.45–2.04)</td>
<td>1.17 (0.53–2.59)</td>
<td>0.76 (0.35–1.66)</td>
</tr>
<tr>
<td>≤1 cup/d</td>
<td>Event no. /at risk</td>
<td>17/149</td>
<td>22/305</td>
<td>15/230</td>
<td>20/459</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>0.93 (0.45–1.92)</td>
<td>0.95 (0.48–1.86)</td>
<td>0.85 (0.41–1.77)</td>
<td>0.62 (0.31–1.23)</td>
</tr>
<tr>
<td>2–3 cups/d</td>
<td>Event no. /at risk</td>
<td>30/257</td>
<td>20/361</td>
<td>18/271</td>
<td>19/500</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>0.98 (0.52–1.86)</td>
<td>0.59 (0.30–1.16)</td>
<td>0.81 (0.40–1.64)</td>
<td>0.49 (0.24–0.99)</td>
</tr>
<tr>
<td>≥4 cups/d</td>
<td>Event no. /at risk</td>
<td>33/437</td>
<td>36/504</td>
<td>14/351</td>
<td>15/492</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>0.72 (0.38–1.35)</td>
<td>0.74 (0.40–1.38)</td>
<td>0.42 (0.20–0.88)</td>
<td>0.37 (0.18–0.77)</td>
</tr>
</tbody>
</table>

Multivariate adjustments include age, sex, BMI, diabetes duration, current smoking habit, current alcohol intake, LTPA, sleep duration, HbA1c, UACR, systolic blood pressure, LDL cholesterol, history of CVD and cancer. BMI, body mass index; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; LTPA, leisure-time physical activity; UACR, urinary albumin creatinine ratio.
Conversely, in a Dutch population, the Alpha Omega Study involving 4837 patients with prior myocardial infarction determined that consuming more than four cups/day of coffee increased mortality by 21% in diabetic patients, whereas it decreased mortality by 27% in those without diabetes. In the Nurses’ Health Study (7170 female patients with diabetes), habitual coffee consumption was not found to be associated with increased risk of mortality. The UK Biobank (total n=498134 participants) failed to identify a significant association between coffee consumption and mortality in diabetic patients. Most of the above studies were conducted in developed country populations, which have a higher risk of CVD than those in Asia. To our knowledge, the present investigation is the first prospective study to demonstrate a significant association between coffee consumption and reduced mortality in an Asian population with type 2 diabetes.

The mechanisms underlying reduced mortality with green tea and coffee consumption are not fully understood. Green tea contains a number of beneficial substances, including phenolic compounds, theanine, and caffeine. Epigallocatechin gallate is the most prevalent phenolic compound: it has been shown to have antioxidant, anti-inflammatory, and anti-mutagenic properties. Coffee also contains numerous bioactive components, including phenolic compounds and caffeine, which have been suggested as contributing to the associated favorable effects. Phenolic compounds, such as chlorogenic acid, have been reported to have a health impact through various mechanisms, such as antioxidant and anti-inflammatory actions.

Caffeine is one of the components in green tea and coffee that could contribute to their favorable effects. The beneficial effects of caffeine on insulin sensitivity and glucose-induced insulin secretion have been suggested through several mechanisms, including weight loss and thermogenesis. However, previous studies have found that consumption of both caffeinated and decaffeinated coffee was associated with reduced mortality. That could mean that caffeine does not play a beneficial role in the association between coffee consumption and risk of mortality. Caffeine has also been reported to stimulate sympathetic activity and increase serum catecholamine levels, leading to increased blood pressure or CVD risk.

The impact of coffee consumption on mortality was greater in the present study (HR 0.58) than that previously reported in developed country diabetic patients: HR 0.81 in men, HR 0.76, and HR 0.53 in women. The difference may be explained by coffee having harmful effects among patients at higher CVD risk: that is based on findings that higher coffee consumption increased mortality among diabetic patients with previous myocardial infarction. Japanese type 2 diabetes patients are generally at lower CVD risk than developed ones; thus, caffeine may exert less detrimental effects on the vasculature, resulting in enhanced beneficial effects of coffee.

To date, no study has investigated the combined effect of green tea and coffee consumption on all-cause mortality. The present study determined that combined higher green tea and coffee consumption markedly reduced mortality. The Japan Public Health Center-Based Study found that the combination of ≥2 cups/day of green tea and ≥1 cup/day of coffee significantly reduced the risk for cerebral infarction and intracerebral hemorrhage. However, that effect did not apply to CHD; the study found no impact on CHD mortality. We found that the relative risk reduction of mortality (HR, 0.37) was greater than when consuming only green tea (HR, 0.72) or only coffee (HR, 0.76; figure 1, table 3), thus, the protective mechanisms of the two beverages may differ. In addition to CVD and cancer, coffee reportedly confers health benefits with liver disease and dementia; however, reduced mortality associated with green tea is mostly explained with respect to CVD or cancer. Green tea and coffee consumption may be associated with different disease incidence or severity.

One strength of the present study is the high follow-up rate (99.5%), which enabled us to accurately investigate the association among green tea and coffee consumption and mortality. Further, this cohort study included potential confounders, such as sleep duration, diabetic complications, lifestyle, physical activity, laboratory data, and medications.

Some limitations of this study deserve mention. First, green tea and coffee consumption was assessed using single, self-reported data, which raises the problem of potential misclassification. However, the green tea and coffee consumption evaluated using our questionnaire showed high correlation with that found with 16 non-consecutive dietary records in a Japanese population. Second, we did not obtain information about some other confounding factors, such as educational and socioeconomic levels. Higher educational or income levels may be associated with greater coffee consumption: they may also be related to lower mortality risk. Those factors may be considered by adjusting for physical activities or smoking status, which could be associated with higher educational or income levels. However, a universal health insurance system has been established in Japan, thus, medical care is supposedly received regardless of educational or socioeconomic states. Third, the CVD medications differed among the coffee groups (table 1). Those medications were not considered in the analyses, however, history of CVD was included as a confounding factor. Fourth, we did not assess whether coffee was caffeinated or decaffeinated. However, decaffeinated coffee is uncommon in Japan. Previous studies have found a similar association between caffeinated or decaffeinated coffee and mortality. Fifth, owing to the observational nature of the present study, we cannot conclude that consuming green tea or coffee reduces mortality. But long-term interventional studies of this kind may be difficult to implement: green tea and coffee are typically consumed as part of daily life.
number of cause-specific deaths was relatively small. That could lead to low statistical power in detecting significant associations. Seventh, there may have been multiple testing problems in our statistical analyses. Multiple testing corrections were not conducted in the present study, however, the results of table 2 are evidently consistent with those of previous studies. Finally, this study was conducted only among a Japanese population. The ingredients of Japanese green tea could differ from those in green tea in other countries. Accordingly, the findings of this study may not apply to other populations.

In conclusion, this prospective cohort study demonstrated that greater consumption of green tea and coffee was significantly associated with reduced all-cause mortality: the effects may be additive. Our results suggest that consuming green tea and coffee may have beneficial effects on the longevity of Japanese people with type 2 diabetes.

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Contributors YK and MI were responsible for the study concept and design. YK, MI, and HF conducted the analysis. TQ, HI, TJ-K, MY, YO, TH, UN, and TK interpreted the data and contributed to the discussion. YK and MI drafted the manuscript. All authors participated in critically reviewing the manuscript and approved the final version. MI is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Patient consent for publication Not required.

Ethics approval The Kyushu University Institutional Review Board (approval number 290). All participants provided their written informed consent to take part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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REFERENCES


Drinking green tea and coffee daily linked to lower death risk in people with diabetes

4 or more cups of green tea + 2 or more of coffee linked to 63% lower all cause mortality

Drinking plenty of both green tea and coffee is linked to a lower risk of dying from any cause among people with type 2 diabetes, suggests research published in the online journal *BMJ Open Diabetes Research & Care*.

Drinking 4 or more daily cups of green tea plus 2 or more of coffee was associated with a 63% lower risk of death over a period of around 5 years, the findings show.

People with type 2 diabetes are more prone to circulatory diseases, dementia, cancer, and bone fractures. And despite an increasing number of effective drugs, lifestyle modifications, such as exercise and diet, remain a cornerstone of treatment.

Previously published research suggests that regularly drinking green tea and coffee may be beneficial for health because of the various bioactive compounds these beverages contain.

But few of these studies have been carried out in people with diabetes. The researchers therefore decided to explore the potential impact of green tea and coffee, separately and combined, on the risk of death among people with the condition.

They tracked the health of 4923 Japanese people (2790 men, 2133 women) with type 2 diabetes (average age 66) for an average of just over 5 years.

All of them had been enrolled in The Fukuoka Diabetes Registry, a multicentre prospective study looking at the effect of drug treatments and lifestyle on the lifespan of patients with type 2 diabetes.

They each filled in a 58-item food and drink questionnaire, which included questions on how much green tea and coffee they drank every day. And they provided background information on lifestyle factors, such as regular exercise, smoking, alcohol consumption and nightly hours of sleep.

Measurements of height, weight and blood pressure were also taken, as were blood and urine samples to check for potential underlying risk factors.

Some 607 of the participants didn’t drink green tea; 1143 drank up to a cup a day; 1384 drank 2-3 cups; and 1784 drank 4 or more. Nearly 1000 (994) of the participants didn’t drink coffee; 1306 drank a cup every day; while 1660 drank 2 or more cups.

During the monitoring period, 309 people (218 men, 91 women) died. The main causes of death were cancer (114) and cardiovascular disease (76).

Compared with those who drank neither beverage, those who drank one or both had lower odds of dying from any cause, with the lowest odds associated with drinking higher quantities of both green tea and coffee.

Drinking up to 1 cup of green tea every day was associated with 15% lower odds of death; while drinking 2-3 cups was associated with 27% lower odds. Getting through 4 or more daily cups was associated with 40% lower odds.
Among coffee drinkers, up to 1 daily cup was associated with 12% lower odds; while 1 cup a day was associated with 19% lower odds. And 2 or more cups was associated with 41% lower odds.

The risk of death was even lower for those who drank both green tea and coffee every day: 51% lower for 2-3 cups of green tea plus 2 or more of coffee; 58% lower for 4 or more cups of green tea plus 1 cup of coffee every day; and 63% lower for a combination of 4 or more cups of green tea and 2 or more cups of coffee every day.

This is an observational study, and as such, can’t establish cause. And the researchers point to several caveats, including the reliance on subjective assessments of the quantities of green tea and coffee drunk.

Nor was any information gathered on other potentially influential factors, such as household income and educational attainment. And the green tea available in Japan may not be the same as that found elsewhere, they add.

The biology behind these observations isn’t fully understood, explain the researchers. Green tea contains several antioxidant and anti-inflammatory compounds, including phenols and theanine, as well as caffeine.

Coffee also contains numerous bioactive components, including phenols. As well as its potentially harmful effects on the circulatory system, caffeine is thought to alter insulin production and sensitivity.

“This prospective cohort study demonstrated that greater consumption of green tea and coffee was significantly associated with reduced all-cause mortality: the effects may be additive,” the researchers conclude.