Abstract

Objective: To examine the association of water intake with risk of mortality from CVD.

Design: Prospective cohort study.

Setting/Subjects: A total of 22,939 men and 35,362 women aged 40–79 years enrolled in the Japan Collaborative Cohort (JACC) Study with available data regarding water intake from foods and beverages. The underlying causes of death were determined based on the International Classification of Diseases.

Results: During the median 19·1 years of follow-up, 1637 men and 1707 women died from CVD. There was an inverse trend between high water intake and risk of CVD in both sexes. Compared with participants in the lowest quintile of water intake, the multivariable-adjusted hazard ratios (95 % CI) for mortality from total CVD in the highest quintile of water intake were 0·88 (0·72, 1·07; P for trend = 0·03) in men and 0·79 (0·66, 0·95; P for trend = 0·10) in women. Those for CHD were 0·81 (0·54, 1·21; P for trend = 0·06) in men and 0·60 (0·39, 0·93; P for trend = 0·20) in women. Reduced risk of mortality from ischaemic stroke was also observed among women in the highest water intake quintile: 0·70 (0·47, 0·99; P for trend = 0·19). There was no association between water intake and mortality from haemorrhagic stroke in either sex.

Conclusions: Higher intake of fluids from foods and beverages was associated with reduced risk of cardiovascular mortality in both sexes and reduced risk of ischaemic stroke in women in Japan.
preventing vasovagal reaction rather than changing the blood volume\textsuperscript{18,19}.

Therefore, the aim of the present study was to examine the association between water intake from foods and beverages and risk of cardiovascular mortality. We gave specific attention to the association with cardiovascular mortality because the water level in the body is associated with vascular contractility via controlling arginine vasopressin hormone\textsuperscript{20}. Yet, current evidence on the water intake–cardiovascular mortality association is inconclusive. Some studies reported an inverse association between water intake and mortality from CVD\textsuperscript{14,21}, while other studies showed no association\textsuperscript{13,15,22,23}.

We hypothesized that higher water intake from foods and beverages is associated with lower risk of mortality from CVD and tested this hypothesis in a large cohort study of Japanese men and women who participated in the Japan Collaborative Cohort (JACC) Study.

\section*{Participants and methods}

\subsection*{Study population}

The JACC Study is a large prospective study started in 1988–1990 and included a total of 110 792 participants (46 465 men and 64 327 women) aged 40–79 years from forty-five Japanese communities. Informed consent was obtained from participants or community leaders, and the ethics committees of Hokkaido University and Osaka University approved the protocol of this study. The sampling methods and protocols of the JACC Study are described in detail elsewhere\textsuperscript{24}.

A total of 24 366 men and 37 421 women completed a self-administered questionnaire about their lifestyles and medical histories that included a forty-food-item FFQ at baseline\textsuperscript{24}. We excluded 1427 men and 2059 women who had a self-reported history of CVD or cancer, as well as medical histories that included a forty-food-item FFQ at baseline\textsuperscript{24}. We excluded 1427 men and 2059 women who had a self-reported history of CVD or cancer, as well as history of chronic kidney disease. Therefore, 22 939 men and 35 362 women were enrolled in the present study.

\subsection*{Dietary assessment}

The FFQ asked about the usual food intake frequency over the past year, without specifying portion size. The five possible frequency responses offered for each food item were: rarely, 1–2 times/month, 1–2 times/week, 3–4 times/week and almost every day\textsuperscript{24}. The consumption of each food item was calculated by multiplying the frequency score of consumption by 0, 0.38, 1.5, 3.5 and 7.0/week, respectively. Water intake was estimated from dietary records for energy-adjusted values and its reproducibility was tested by applying the same FFQ after one year in a sub-sample of eighty-five participants\textsuperscript{20}. The Spearman rank-correlation coefficient for the validity of the FFQ-estimated water intake from foods and beverages with reference to the dietary-record water intake from foods and beverages was 0.41 and 0.71 for the two FFQ. The estimated mean water intake was 1317 ml/d according to the FFQ and 1318 ml/d according to the four seasonal 3d dietary records.

\subsection*{Mortality surveillance}

Investigators conducted a systematic review of death certificates as part of the mortality surveillance in each community. Mortality data were forwarded to the public health departments of the respective areas before being centralized at the Ministry of Health and Welfare, and the underlying causes of death were coded in accordance with the International Classification for Diseases, 10th revision (ICD-10). Participants who died after moving out of their original communities were treated as censored cases. The primary end points for the current analysis were deaths from stroke (ICD-10 codes I60–I69), haemorrhagic stroke (ICD-10 codes I60–I61), ischaemic stroke (ICD-10 code I63), CHD (ICD-10 codes I20–I25) and total CVD (ICD-10 codes I01–I99).

\subsection*{Statistical analysis}

Age-adjusted mean values and proportions of mortality risk factors and participants’ characteristics across sex-specific quintiles of water intake (<1053, 1053–1250, 1251–1442, 1443–1690 and ≥1691 ml/d for men; <1036, 1036–1220, 1221–1393, 1394–1606 and ≥1606 ml/d for women) were calculated and the differences in those variables across the increasing quintiles of intake were tested by ANCOVA and the \( \chi^2 \) test. Statistical analyses were based on mortality during the follow-up period and the person-years of follow-up was defined as the period from submission of the initial baseline questionnaire to death, departure of a participant from his/her original...
community or termination of follow-up at the end of 2009, whichever came first.

Using the lowest quintile of water intake (<1053 ml/d for men; <1036 ml/d for women) as the reference category, the sex-specific hazard ratios (HR) and their 95% CI for mortality outcomes were calculated by Cox proportional hazards modelling after adjustment for age. The multivariable model was further adjusted for sex-specific quintiles of BMI, smoking status (never, ex-smoker, current smokers of 1–19 and ≥20 cigarettes/d), alcohol intake category (never, ex-drinker, current drinkers of 1–22, 23–45, 46–68 and ≥69 g ethanol/d), history of hypertension and diabetes (yes or no), hours of exercise (almost never, 1–2, 3–4 and ≥5 h/week), hours of walking (almost never, 1–2, 3–4 and ≥5 h/week), hours of sleep (<6, 6–7 and ≥8 h/d continuous), education levels (primary school, junior high school, high school, college or more), perceived mental stress (low, medium, high), dietary sugar and fibre intakes (g/d, sex-specific quintiles); as well as intake frequencies of fresh fish, vegetables and fruits (almost never, 1–2 times/month, 1–2 times/week, 3–4 times/week, almost every day), green tea (almost never, 1–4 times/week, 1–2, 3–9 and ≥10 times/d) and coffee (almost never, 1–2 times/month, 1–2 and 3–4 times/week, 1–2 and ≥3 times/d). We conducted tests for trends across quintiles of water intake by assigning median values for each quintile and testing the significance of this variable.

We further analysed the data after exclusion of persons who died within the first 5 years of follow-up to examine a potential effect of as-yet-undiagnosed diseases at baseline. Another sensitivity analysis was conducted by excluding participants with a history of diabetes mellitus at the study baseline. We also tested if the associations between the reported water intake and the risk of mortality from CVD varied by the season when the participants responded to the questionnaire. Probability values for statistical tests were two-tailed and \( P < 0.05 \) was regarded as statistically significant. The SAS statistical software package version 9.4 was used for the analyses.

**Results**

During the 19.1-year median follow-up for 22939 men, there were 1637 deaths from total CVD that included 720 deaths from total strokes (234 haemorrhagic strokes and 425 ischaemic strokes) and 390 from CHD. The respective numbers of deaths among 35362 women were 1707, 777 (315 and 384) and 305.

Compared with participants in the lowest quintile of water intake, men in the highest quintile were slightly older and consumed more sugar, while women with the highest quintile were slightly younger, more likely to smoke and to practise sports, but less likely to be diabetic and consumed less sugar (Table 1). Water intake was positively associated with intakes of coffee, green tea, fresh fish, vegetables, fruits and fibre and with education levels for both men and women, while it was inversely associated with alcohol consumption, hours of sleep and history of hypertension in men and women. There was no association between water intake and BMI in either sex.

Table 2 shows age- and multivariable-adjusted HR (and 95% CI) of mortality from CVD according to quintile of water intake from foods and beverages. Compared with participants in the lowest quintile of water intake, both men and women in the highest quintile of intake had lower risks of mortality from CHD and total CVD. In men, the multivariable-adjusted HR (95% CI) were 0.81 (0.54, 1.21; \( P \) for trend = 0.06) for CHD and 0.88 (0.72, 1.07; \( P \) for trend = 0.03) for total CVD. The respective values in women were 0.60 (0.39, 0.93; \( P \) for trend = 0.20) and 0.79 (0.66, 0.95; \( P \) for trend = 0.10). Reduced risk of mortality from ischaemic stroke was also observed for women in the highest quintile of intake: 0.70 (0.47, 0.99; \( P \) for trend = 0.19); but not in men: 0.89 (0.60, 1.31; \( P \) for trend = 0.68).

Excluding early deaths within 5 years from baseline or participants with diabetes at baseline did not change the associations materially (see online supplementary material, Supplemental Tables 1 and 2). There were no differences in the reported association between participants who returned the questionnaire in summer, autumn, winter and spring. There was no association between water intake and mortality from haemorrhagic stroke in either sex.

**Discussion**

In the present large prospective cohort study, water intake from foods and beverages was associated with reduced risk of mortality from CHD and total CVD in Japanese men and women; moreover, higher water intake was associated with reduced risk of mortality from ischaemic stroke among women but not men. These associations were independent of age, BMI, intakes of coffee, tea, vegetables, fruits and alcohol, total energy intake and other mortality risk factors.

To the best of our knowledge, the present study is the first to show that higher water intake from foods and beverages is associated with reduced risk of mortality from CHD and ischaemic stroke in the Japanese population. Among 120852 men and women aged 55–69 years of the Netherlands Cohort Study during the 10 years of follow-up, higher total fluid intake (plain water plus moisture from foods and beverages: >2.0 v. <1.0 litres/d) tended to be associated with reduced risk of mortality from total stroke but not from CHD. The multivariable-adjusted HR (95% CI) for mortality from total stroke were 0.77 (0.45, 1.30) in men and 0.60 (0.31, 1.15) in women, and those for CHD mortality were 1.03 (0.73, 1.47) and 1.04 (0.67, 1.61), respectively. The Blue Mountains Eye Study of 3858 men and women aged 49 years or older showed that fluid...
intake from foods and beverages was not associated with cardiovascular mortality; the multivariable-adjusted HR (95 % CI) in the highest v. lowest quartile of water intake (≥3 v. <2 litres/d) was 0.91 (0.70, 1.19)\(^{22}\). Similarly, the third National Health and Nutrition Examination Survey (NHANES III) indicated that higher total fluid intake (plain water plus moisture from foods and beverages) was not associated with mortality from CVD; the multivariable-adjusted HR (95 % CI) in the highest v. lowest quartile (≥3.6 v. < 2.1 litres/d) of total fluid intake was 0.99 (0.75, 1.29)\(^{15}\).

Regarding plain water intake, on the other hand, during the 6-year follow-up of 20 297 American men and women aged 38–100 years of the Adventist Health Study, higher plain water intake was associated with a reduced risk of mortality from CHD; the multivariable-adjusted HR (95 % CI) for the highest plain water intake (≥5 v. ≤2 glasses/d) was 0.39 (0.22, 0.67; \(P\) for trend = 0.003) in men and 0.52 (0.27, 1.03; \(P\) for trend = 0.17) in women\(^{14}\). In addition, during the 10-year follow-up of 120 852 men and women aged 55–69 years of the Netherlands Cohort Study, high plain water intake (≥500 ml/d v. zero) tended to be associated with a reduced risk of mortality from total stroke; the multivariable-adjusted HR (95 % CI) was 0.85 (0.31, 2.29) in men and 0.49 (0.19, 1.24) in women\(^{21}\).

Many factors interact to determine the amount of fluid intake; one of which is the season. A previous Japanese study reported that water intake was highest in summer (2331 g/d) and lowest in winter (2134 g/d), and the intake of water from beverages including plain water increased by 8.4 g/d while that from foods decreased by 3.1 g/d with each 1°C increase in mean outdoor air temperature\(^{10}\). In our study, we could not find any effect modification by the season when the questionnaire was administered on the association of water intake from foods and beverages with cardiovascular mortality. The FFQ in our study inquired about the intake over the last 12 months; therefore, the collected dietary intakes including water from foods and beverages was not adjusted with season when the questionnaire was administered on the study period.
browns were not confined to a specific season but were the overall intakes over one year.

The proportion of plain water intake out of total fluid intake has been shown to be variable among populations (7-11). For example, this proportion was 35% in US participants in the NHANES 2005–2006 (7), 54% in Korean participants in the National Health and Nutrition Examination Survey (KNHANES) 2008–2012 (9) and 53% in adult dwellers of four cities in China (10). Unfortunately, we do not have data on the consumption of plain water in our study to state what percentage is accounted for by plain water. Even the Japan National Health and Nutrition Survey, a survey conducted annually by the Japanese Ministry of Health, Labour, and Welfare to understand the status of people’s health, nutritional intake and lifestyle habits, has not published any data about the proportions of plain water and water from foods and beverages. Thus, we were unable to discern any potential differences described in previous studies regarding the associations of water intake from foods and beverages as opposed to plain water intake with cardiovascular mortality. However, small Japanese studies have reported the proportions of water intake from different sources. For example, in a study conducted in four areas in Japan with a total of 121 women aged 30–69 years and 121 men aged 30–76 years who completed 16d diet records, the mean total water intake was 2230g/d and almost half of the water was derived from foods (1130 g/d), the remaining half coming from beverages including plain water (1130 g/d) (101). In another study among 3855 female Japanese dietetic students aged 18–20 years from fifty-three institutions in Japan, the mean total daily water intake (g/4186kJ) was 1028g; 654g from fluids including plain water and 374g from foods (5). A report from thirteen countries that collected 7d fluid-specific records showed a total fluid intake from beverages of 1.5 litres/d in 1318 Japanese men and

### Table 2 Hazard ratio (HR) and 95% CI of mortality from CHD, total stroke, stroke type and total CVD, according to quintile of water intake from foods and beverages, among 22,939 men and 35,362 women aged 40–79 years, Japan Collaborative Cohort (JACC) Study

<table>
<thead>
<tr>
<th>Quintiles of energy-adjusted water intake</th>
<th>1 (low)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5 (high)</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref</td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
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<tr>
<td><strong>Men</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Total CVD, n</td>
<td></td>
<td></td>
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<tr>
<td>Age-adjusted</td>
<td>1.00</td>
<td>0.97</td>
<td>0.86</td>
<td>1.09</td>
<td>0.95</td>
<td>0.85</td>
</tr>
<tr>
<td>Multivariable-adjusted†</td>
<td>1.00</td>
<td>1.00</td>
<td>0.86</td>
<td>1.18</td>
<td>1.01</td>
<td>0.85</td>
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<td>CHD, n</td>
<td></td>
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<td></td>
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<tr>
<td>Age-adjusted</td>
<td>1.00</td>
<td>1.00</td>
<td>0.80</td>
<td>1.27</td>
<td>0.97</td>
<td>0.76</td>
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<tr>
<td>Multivariable-adjusted†</td>
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<td>1.02</td>
<td>0.74</td>
<td>1.40</td>
<td>1.05</td>
<td>0.75</td>
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<tr>
<td>Total stroke, n</td>
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<td>138</td>
<td>137</td>
<td>137</td>
<td>148</td>
<td>139</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.00</td>
<td>0.97</td>
<td>0.81</td>
<td>1.16</td>
<td>0.97</td>
<td>0.81</td>
</tr>
<tr>
<td>Multivariable-adjusted†</td>
<td>1.00</td>
<td>0.97</td>
<td>0.76</td>
<td>1.23</td>
<td>1.02</td>
<td>0.79</td>
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<tr>
<td><strong>Women</strong></td>
<td></td>
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<tr>
<td>Total CVD, n</td>
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<tr>
<td>Age-adjusted</td>
<td>1.00</td>
<td>0.85</td>
<td>0.62</td>
<td>1.18</td>
<td>0.92</td>
<td>0.68</td>
</tr>
<tr>
<td>Multivariable-adjusted†</td>
<td>1.00</td>
<td>0.84</td>
<td>0.55</td>
<td>1.28</td>
<td>0.97</td>
<td>0.62</td>
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<tr>
<td>Ischaemic stroke, n</td>
<td>82</td>
<td>85</td>
<td>81</td>
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<td>88</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.00</td>
<td>1.04</td>
<td>0.82</td>
<td>1.31</td>
<td>1.02</td>
<td>0.81</td>
</tr>
<tr>
<td>Multivariable-adjusted†</td>
<td>1.00</td>
<td>1.09</td>
<td>0.79</td>
<td>1.50</td>
<td>1.10</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Ref, reference category. *P<0.05. **P<0.01. ***P<0.001.
†Adjusted for age, BMI (quintile), smoking, alcohol consumption, intakes of coffee, green tea, fresh fish, vegetables, fruits, fibre, sugar and energy, hours of sleep, walking and sports, education level and history of hypertension and diabetes mellitus.
women aged 18 years or older, and 18% of this amount was consumed as plain water\(^{11}\).

Mechanisms by which water intake is associated with reduced risk of mortality from CVD are not well known. However, the vasopressin system might play a role. Post myocardial infarction activation of the vasopressin system was reported in an observational study of 980 patients. Copeptin, the C-terminal part of the vasopressin prohormone, and N-terminal pro-B-type natriuretic peptide (NTproBNP), an established marker for left ventricular function and the prognosis of myocardial infarction, were at highest levels at admission then plateaued within 3–5 days; moreover, their levels were higher in patients who died or were readmitted for heart failure than in survivors\(^{20}\).

Another mechanism was shown in a clinical trial of 293 healthy men and women aged 20–95 years which demonstrated that hypo-hydration leads to high blood viscosity\(^{27}\), which was positively associated with 8-year risk of CHD among 933 men aged 45–64 years of the MONICA-Augsburg cohort study\(^{28}\). Among 4112 men and women aged ≥20 years in NHANES 1999–2006, individuals with high water intakes either from plain water or from foods and beverages had healthier lifestyles, such as high physical activity, high education and high fibre intake, and lower sugar intake, than individuals with low water intakes\(^{29}\). In the present study, however, the reduced risk of mortality from CVD associated with high fluid intake remained statistically significant after adjustment for education level, fibre and sugar intakes.

The strengths of our study include its prospective design, the use of a validated FFQ, the consistent way of end-point determination and its large sample size from community residents. In addition, the exclusion of persons with known chronic diseases at baseline reduced bias arising from dietary changes due to known morbidity. We even took account of the possibility that preclinical diseases may affect water intake or that prevalent diabetes may increase water intake due to thirst, and we examined the association after excluding early deaths within 5 years from baseline and participants with diabetes at baseline; there was, however, no material change in the findings.

Limitations of the current study include the above-discussed lack of estimation of total fluid consumption including plain water intake. Unfortunately, none of the previous studies that assessed the associations of intakes of both plain water and water from foods and beverages with risk of CVD\(^{14,15,21,22}\) have reported the correlations between plain water intake and that from foods and beverages in their samples. However, among 2691 US adults aged ≥20 years from the NHANES 2005–2006, plain water was positively associated with moisture in foods and inversely associated with moisture in beverages. Moreover, it was suggested that outdoor temperature can affect the proportions of water intake from foods, beverages and plain water\(^{10}\). Although we found no effect modification by the season when the questionnaire was administered on the association of water intake from foods and beverages with cardiovascular mortality, further studies are needed to investigate the associations between water intakes from various sources and risk of CVD.

**Conclusion**

In conclusion, high intake of water from foods and beverages was associated with reduced risk of cardiovascular mortality for both sexes and reduced risk of ischaemic stroke for women in Japan.

**Acknowledgements**

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*Authorship:* H.I. and A.T. designed this research; R.C. and E.S.E. conducted the analyses and prepared the manuscript; H.I., K.M. and A.T. critically revised the manuscript; H.I. and A.T. had primary responsibility for the final content. All authors read and approved the final manuscript.

*Ethics of human subject participation:* This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the ethics committees of Hokkaido University and Osaka University. Informed verbal consent was obtained from all subjects; in a few study areas, the consent was obtained from the area representative (the ‘mayor’) after explaining the purpose of the study.

**Supplementary material**

To view supplementary material for this article, please visit https://doi.org/10.1017/S1368980018001386

**References**

Water intake from foods & beverages & mortality risk