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ORIGINAL RESEARCH

Impact of Fruit and Fruit Juice on Death and Disease Incidence: A Sex-Specific Longitudinal Analysis of 18 603 Adults

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BACKGROUND: The health benefits of fruits are well established, but fruit juice has been more controversial. Fruit and juice are often ingested with other foods, which prompted our investigation to determine whether fruit consumed as juice may negate the beneficial effects of consuming whole fruit in people with cardiovascular disease.

METHODS AND RESULTS: We retrospectively analyzed data from a population-based study in Australia (the 45 and Up Study) linked with hospitalization and mortality data up to September 2018. Kaplan-Meier survival estimates and Cox proportional hazards models were used to examine effects of fruit, fruit juice, and the combination of fruit and fruit juice in relation to death and disease incidence among men and women living with cardiovascular disease. A total of 7308 deaths occurred among 18 603 participants diagnosed with cardiovascular disease over a 13-year follow-up. After multivariable adjustment, inadequate fruit intake (hazard ratio [HR], 1.12 [95% CI, 1.01–1.24]) and high fruit juice intake (HR, 1.26 [95% CI, 1.12–1.41]) predicted all-cause mortality in women. Also, high fruit juice intake plus either adequate fruit intake (HR, 1.18 [95% CI, 1.02–1.37]) or inadequate fruit intake (HR, 1.43 [95% CI, 1.21–1.69]) predicted mortality in women. No relationships were found in men after multivariable adjustments. Also, we found no prognostic value for fruit and fruit juice intake on disease incidence.

CONCLUSIONS: In adults with cardiovascular disease, we found that fruit juice (in combination with adequate or inadequate fruit intake) predicted mortality in women but not in men. These effects became less clear when focusing on disease incidence.

Key Words: cardiovascular disease ■ death ■ fruit ■ fruit juice ■ secondary prevention ■ sex specific

See Editorial by Minissian.

Accumulating epidemiological studies and substantial experimental studies have supported the health benefits of whole fruit in terms of overall health and cardioprotection given that fruit is abundant in vitamins, minerals, and phytochemicals.[1,2] Although the benefits of fruits are well established, the health effects of fruit juice have been controversial.[3–6] International dietary guidelines are not in agreement on the inclusion of fruit juice.[7] For example, the guidelines from the United States and United Kingdom recognize the benefit of 100% fruit juice and recommend that daily fruit intake can be partly replaced by 100% fruit juice.[8] However, other countries, such as Australia, promote a more prudent attitude by only recommending occasional fruit juice consumption[9] with a serving size of 125 mL of 100% juice replacing a half serving of fruit.

In real life, it is common for people to consume both fruit and fruit juice within a single day. People may consume a glass of fruit juice with a meal[10] while also eating separate servings of whole fruits with or between meals. Fruit juice consumption is associated with

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RESEARCH PERSPECTIVE

What Is New?

- Our research examined the impact of fruit and fruit juice consumption, specifically exploring whether additional fruit juice intake, in combination with adequate fruit consumption, affects overall or cardiovascular health.
- Our findings need to be confirmed in other population-based studies to allow sufficient consistent evidence for policy solutions to promote healthy eating.

What Question Should Be Addressed Next?

- Further exploration of the long-term effect of fruit juice intake on cardiovascular disease should be conducted, specifically focusing on secondary prevention, in men and women and in different ancestries.

an overall better diet quality,[5] thus it is possible that people who drink fruit juice also have more adequate fruit intake than those who do not. However, studies usually overlook the joint effects of fruit and fruit juice consumption, with limited information available to understand how additional fruit juice along with adequate fruit intake affects overall or cardiovascular health.

This debate may be particularly important in people with increased cardiovascular risk. Dietary recommendations on the joint effects of fruit and fruit juice in people living with cardiovascular disease (CVD) are unclear. It is also well known that dietary preferences that impact cardiovascular risk vary substantially between men and women. For example, we have previously shown sex disparities in preferences for specific types of milk consumption, and explored how these differences were associated with cardiovascular deaths. Forty-eight percent of men preferred reduced fat milk, whereas 40.3% consumed whole milk. In comparison, 53.6% of women commonly consumed reduced fat milk, whereas 31% consumed whole milk. These differences resulted in a greater risk of cardiovascular deaths for men compared with women.[11] However, limited studies have reviewed sex differences in whole fruit and juice intake and how they predict death and disease incidence.[11] We therefore examined the effects of fruit and fruit juice separately and their joint effects in relation to mortality and other disease incidence among men and women with CVD. In addition, given that limited studies have reviewed the long-term consumption effects of whole fruit and fruit juice,[11] we also performed an analysis with the aim to understand long-term effects of fruit and fruit juice in relation to mortality and other disease incidence.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the Sax Institute at 45andup.research@saxinstitute.org.au.

Data Sources

This research used the established Central and Eastern Sydney Primary and Community Health Cohort/Linkage Resource based on the Sax Institute's 45 and Up Study[12] and New South Wales health administrative data by the Centre for Health Record Linkage.[13] The Centre for Health Record Linkage uses a probabilistic procedure to link records, in which records with an uncertain probability of being true matches are checked by hand. Its current estimated false-positive rate is 0.5%.[14]

The 45 and Up Study is a large-scale Australian cohort study including 267 357 men and women aged ≥45 years across New South Wales, Australia. The baseline participants were recruited and surveyed between 2005 and 2009, representing about 11% of this age group. Upon recruitment, participants provided consent for future follow-up. The first follow-up survey data were collected between 2012 and 2015. At both time points, socioeconomic, health behavior, and health-related information were collected via a comprehensive questionnaire. About 19% of those invited participated, and participants included about 11% of the New South Wales population aged ≥45 years. Details of the 45 and Up Study, including sampling strategy and methods, are described elsewhere.[15]

Data from study participants were linked to the New South Wales Admitted Patient Care Data Collection, providing all public and private hospital admissions in New South Wales (2001–2018). It contains details of participant admission, dates of admission and discharge, the primary reason for admission, up to 55 additional clinical diagnoses using the World Health Organization's *International Classification of Diseases, Tenth Revision, Australian Modification* (*ICD-10-AM*), and up to 59 operations or procedures.[16] Vital status and date of death were ascertained from the date of recruitment up to September 30, 2018 using linkage to the New South Wales Registry of Births, Deaths, and Marriages. Death registrations capture all deaths in New South Wales. Cause of death information was only available until June 30, 2016 at the time of analysis, which was not included in the analysis.

Ethical approval was granted for this research by the New South Wales Population and Health Services Research Ethics Committee (reference number: 2016/06/642) and from the University of New South Wales Human Research Ethics Committee for the 45 and Up Study.

Participant Cohort

The study cohort includes participants diagnosed with CVD, which was defined as the first hospitalization following recruitment into the 45 and Up Study with diagnosis of CVD at discharge, based on the *ICD-10-AM* 3-character codes of I00–I99, G45, and G46.[16] Table S1 presents the detailed breakdown of participants into 8 CVD categories based on the *ICD-10-AM* codes.

For the main analysis, we included participants diagnosed with CVD (identified from Admitted Patient Care Data Collection data) before the 45 and Up Study baseline survey, and who had completed the baseline survey (2005–2009) on dietary consumption. Participants who had self-reported heart disease at the baseline survey were also included. For the sensitivity analysis, we included participants diagnosed with CVD, and who have completed both baseline (2006–2009) and follow-up surveys (2012–2015) on dietary consumption to identify long-term dietary behavior.

Outcomes: Mortality and Disease Incidence

For the outcome of mortality, participants were followed until their date of death (according to the latest available mortality data) or the end of follow-up (ie, September 30, 2018), whichever came first. With a total of 18 603 participants diagnosed with CVD and with complete baseline data, there were 7308 deaths (men: 4756, women: 2552) until September 30, 2018.

For the outcome of disease incidence, participants were followed until their date of the disease occurs (ie, first hospitalization record) or the end of follow-up, whichever came first. We also tested the effects of fruit and fruit juice in relation to other chronic conditions for the following 2 reasons: (1) Strong associations between diet and various chronic diseases have been widely reported. (2) The occurrence of comorbidities, defined as the presence of 2 or more chronic conditions, is common among the older individuals in our study cohort, who have a mean age of 71 years. Among a total of 21 categories in *ICD-10-AM* codes, 13 disease categories can be generally identified as chronic conditions. Those are: (1) neoplasms (C00–D48), (2) diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50–D99), (3) endocrine, nutritional and metabolic diseases (E00–E99), (4) mental, behavioral, and neurodevelopmental disorders (F00–F99), (5) diseases of the nervous system (G00–G99), (6) diseases of the eye and adnexa (H00–H59), (7) diseases of the ear and mastoid process (H60–H99), (8) diseases of the circulatory system (I00–I99), (9) diseases of the respiratory system (J00–J99), (10) diseases of the digestive system (K00–K99), (11) diseases of the skin and subcutaneous tissue (L00–L99), (12) diseases of the musculoskeletal system and connective tissue (M00–M99), and (13) diseases of the genitourinary system (N00–N99).[17]

Fruit, Fruit Juice, and the Joint Effect of Fruit and Fruit Juice

In the 45 and Up Study questionnaire, dietary consumption was assessed using short food frequency questions, which promote participants to indicate the frequency of their specific food consumption, commonly reported on a weekly or daily basis. The details have been described in our previous studies.[18–20] Each of the questions on diet was previously validated in the Million Women Study.[21] With regard to fruit and fruit juice intake, the participants were asked: About how many servings of fruit or glasses of fruit juice do you usually have each day? A serving was identified as 1 medium piece or 2 small pieces or 1 cup of diced or canned fruit pieces.

Adequate fruit intake was identified if people consumed >2 servings per day based on the Australian Guide to Healthy Eating.[11] Because there was no specific recommendation on fruit juice intake, we used the median intake as the cutoff to assess fruit juice intake, namely low (<1 glass per day) versus high (≥1 glass per day). To assess the joint effect of fruit and fruit juice, we generated 4 categories for analysis, namely (1) inadequate fruit and low fruit juice intake, (2) adequate fruit and low fruit juice intake, (3) inadequate fruit and high fruit juice intake, and (4) adequate fruit and high fruit juice intake.

Covariates

We included sociodemographic factors, health behavioral factors, and consumption of other food groups as covariates in the statistical analysis. Sociodemographic variables included age, marital status, education, and socioeconomic level. Marital status was categorized as married/partner, single/divorced/separated, and widowed. Education levels were divided into 3 categories: low, no school certificate or other qualification, and school or intermediate certificate; medium, high school or leaving certificate and trade or apprenticeship; and high: certificate or diploma and university degree or higher. Socioeconomic levels were assessed by the Socio-Economic Indexes for Areas, which is based on 3 tertiles (low, medium, high) of the Index of Relative Socioeconomic Advantage and Disadvantage.[22]

Health behaviors included smoking, alcohol drinking, and physical activity levels. Smoking was identified as never smoked, previous smoker, and current smoker based on 2 questions: Have you ever been a regular smoker? Are you a regular smoker now? The frequency of alcohol consumption was identified by

a question about how many alcoholic drinks do you have each week? Physical activity was measured using the Active Australia Survey, asking the total time spent on walking, and on moderate-intensity and vigorous-intensity physical activity in the previous week. Adequate physical activity was identified if people spent 150 minutes of moderate-intensity physical activity, or 75 minutes of vigorous-intensity physical activity per week.[23] Body mass index was also included and calculated based on the weight and height that was identified by the questions: About how much do you weigh? How tall are you without shoes?

Based on the Australian Guide to Healthy Eating,[9] other food components were also included as covariates, namely (1) vegetables, (2) cereal grains, (3) lean meat and poultry, and (4) dairy or dairy alternatives.[18] The frequency of consuming these food groups was reported in the 45 and Up Study dietary questionnaire. We also included self-reported hypertension and diabetes as covariates because of the strong association of these conditions with CVD. The details have been described in our previous publications.[18,19]

Statistical Analysis

Number and percentage for categorical variables and mean (SD) for continuous variables were used to present baseline characteristics by survival status, with sex-specific data representation for men and women. Categories of fruit, fruit juice, and the joint effect of fruit and fruit juice by survival status were also tested for men and women. χ^2 and ANOVA were applied to present statistical differences.

A time-to-event analysis was performed to measure the effects of fruit, fruit juice, and the joint effect of fruit and fruit juice in relation to survival status and incidence of disease among men and women following diagnosis of CVD. The follow-up time started at the baseline interview date and was censored at death, at incidence of disease (by *ICD-10-AM* categories), or September 30, 2018, whichever came first.

Kaplan-Meier survival curves for the 2 categories of fruit and fruit juice consumption, and 4 categories of the joint effect of fruit and fruit juice consumption were generated, and a log-rank test was performed to compare the categories. We also presented results from Cox proportional hazard regression models in the forest plots as crude and adjusted models, with hazard ratio (HR) and 95% CI. The latter model was adjusted for socioeconomic factors (age, marital status, education, and socioeconomic level), health behaviors (smoking, alcohol drinking, physical activity levels), consumption of other foods (vegetables, dairy or alternatives, cereal grains, lean meat and poultry), and other chronic conditions (body mass index, hypertension, and diabetes) given that these variables were commonly reported as related to cardiovascular disease and death. All analyses were conducted in Stata/SE 16 (StataCorp, College Station, TX). We also tested the proportional hazards assumption on the basis of Schoenfeld residuals via Stata using the estat phtest command.

Post Hoc Analyses

We also examined long-term behavior of fruit and fruit juice consumption and its relationship with survival. We performed sensitivity analysis by including participants who completed both baseline and follow-up dietary questionnaires and linked their dietary data to mortality and incident data identified from death registrations and the Admitted Patient Care Data Collection. A total of 7236 participants, with 1101 participants who died, until September 30, 2018 were identified. The study flowchart is shown in Figure S1.

The methodology used to identify long-term fruit and fruit juice consumption is outlined in Table S2, where we provide information on how participants were categorized based on their intake patterns over time to allow examination of their long-term dietary behavior. Cox proportional hazard regression models were also applied to examine long-term consumption of fruit, fruit juice, and the joint effect of fruit and fruit juice intake in relation to mortality and incidence of diseases in the sensitivity analysis and displayed as forest plots. We presented the HR (95% CI) for the crude and adjusted models with adjustments for baseline socioeconomic factors (age, marital status, education, and socioeconomic level), health behaviors (smoking, alcohol drinking, physical activity levels), the consumption of other foods (vegetables, dairy or alternatives, cereal grains, lean meat and poultry), and chronic conditions (hypertension and diabetes).

RESULTS

The baseline characteristics of participants are shown by survival status for men and women in the Table. A total of 18 603 participants (men: 11 295, women: 7308) had a mean follow-up period of 8.4 years (men: 8.4 years, women: 8.5 years). The death rate was 46.6 (95% CI, 45.6–47.7) per 1000 person-years (men: 48.7 [95% CI, 47.3–50.1], women: 43.2 [95% CI, 41.6–44.9]). The data for fruit and fruit juice consumption were normally distributed, with mean (SD) and median (interquartile range) for fruit consumption being 1.98 (1.5) and 2 (1–3) servings per day, and for fruit juice consumption being 0.92 (1.26) and 1 (0–1) glass per day. A greater proportion of men and women with high fruit juice consumption died compared with those with low fruit juice consumption (P<0.001). A lower proportion of men and women with a combined intake of adequate

Table. Baseline Characteristics by Survival Status for Men and Women (N=18 063)

Characteristic	Men			Women		
	Survival status			Survival status		
	Alive	Died	*P* value	Alive	Died	*P* value
Age, y, mean (SD)	66.8 (9.4)	77.4 (8.3)	<0.001*	67.5 (10.1)	79.6 (9.2)	<0.001*
Marital status, n (%)						
Married/partner	5611 (81.9)	3426 (72.9)	<0.001*	2835 (65.1)	1005 (39.7)	<0.001*
Single/divorce/separated/widowed	1234 (18.1)	1272 (27.1)		1521 (34.9)	1525 (60.3)	
Education, n (%)						
Low	2054 (30.3)	1758 (38.6)	<0.001*	2288 (53.4)	1481 (61.1)	<0.001*
Medium	3304 (48.7)	2133 (46.8)		1421 (33.1)	764 (31.5)	
High	1432 (21.0)	663 (14.6)		579 (13.5)	180 (7.4)	
SEIFA†, n (%)						
Low	1952 (29.0)	1652 (35.5)	<0.001*	1502 (35.1)	996 (40.0)	<0.001*
Medium	2294 (34.1)	1544 (33.1)		1427 (33.4)	803 (32.3)	
High	2478 (36.9)	1465 (31.4)		1348 (31.5)	689 (27.7)	
Country of birth, n (%)						
Australian	3602 (52.1)	2504 (52.7)	<0.70	2367 (54.1)	1433 (56.2)	0.22
English	1615 (23.4)	1118 (23.5)		1093 (24.9)	620 (24.3)	
Irish	352 (5.1)	221 (4.7)		240 (5.5)	117 (4.6)	
Others	1347 (19.5)	913 (19.2)		679 (15.5)	382 (14.9)	
Smoking, n (%)						
No	6510 (94.8)	4478 (95.0)	0.61	4164 (95.5)	2434 (96.0)	0.29
Yes	360 (5.2)	237 (5.0)		197 (4.5)	101 (4.0)	
Physical activity‡, n (%)						
Inadequate	1805 (26.5)	2111 (45.8)	<0.001*	1290 (30.2)	1386 (57.7)	<0.001*
Adequate	5014 (73.5)	2496 (54.2)		2988 (69.9)	1016 (42.3)	
Body mass index, mean (SD)	27.8 (4.3)	26.8 (4.7)	<0.001*	28.8 (5.6)	26.1 (5.6)	<0.001*
Diagnose of high blood pressure, n (%)						
No	3162 (45.7)	2192 (46.1)	0.69	1918 (43.8)	1120 (43.9)	0.94
Yes	3754 (54.3)	2564 (53.9)		2461 (56.2)	1432 (56.1)	
Diagnose of diabetes, n (%)						
No	5731 (82.9)	3569 (75.0)	<0.001*	3672 (83.9)	2011 (78.8)	<0.001*
Yes	1185 (17.1)	1187 (25.0)		707 (16.1)	541 (21.2)	
Vegetables, servings, mean (SD)	3.55 (2.7)	3.51 (2.8)	0.51	4.42 (2.8)	3.99 (2.7)	<0.001*
Cereals, bowls, mean (SD)	5.08 (2.7)	5.56 (2.6)	<0.001*	4.96 (2.7)	5.47 (2.6)	<0.001*
Protein, times, mean (SD)	3.99 (2.5)	3.83 (2.7)	<0.001*	4.12 (2.5)	3.7 (2.3)	<0.001*
Dairy, n (%)						
No	276 (4.0)	237 (5.0)	0.01*	170 (3.9)	102 (4.0)	0.81
Yes	6640 (96.0)	4518 (95.0)		4209 (96.1)	2450 (96.0)	
Fruit, n (%)						
Inadequate	3132 (47.4)	2020 (45.3)	0.03*	1443 (34.0)	860 (35.6)	0.17
Adequate	3477 (52.6)	2438 (54.7)		2803 (66.0)	1553 (64.4)	
Fruit juice, n (%)§						
Low, <1 glass	2214 (41.0)	1130 (32.7)	<0.001*	1661 (48.2)	609 (32.1)	<0.001*
High, ≥1 glass	3193 (59.0)	2330 (67.3)		1784 (51.8)	1290 (67.9)	
Fruit and fruit juice, n (%)						
Inadequate fruit, low fruit juice	1125 (21.4)	544 (16.3)	<0.001*	598 (17.5)	224 (12.1)	<0.001*
Inadequate fruit, high fruit juice	1358 (25.8)	955 (28.6)		538 (15.8)	438 (23.6)	

(*Continued*)

Table. Continued

Characteristic	Men			Women		
	Survival status			Survival status		
	Alive	Died	*P* value	Alive	Died	*P* value
Adequate fruit, low fruit juice	1073 (20.4)	572 (17.1)		1056 (31.0)	380 (20.5)	
Adequate fruit, high fruit juice	1700 (32.3)	1269 (38.0)		1218 (35.7)	813 (43.8)	

SEIFA indicates Socioeconomic Indexes for Areas.
*Significant results: $P < 0.05$.
†SEIFA is based on 3 quantiles (low, medium, high) of the Index of Relative Socioeconomic Advantage and Disadvantage.
‡Adequate physical activity was identified if people spent 150 minutes of moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity per week.
§Based on the medium intake of fruit juice as the cutoff.

fruit and low fruit juice died compared with their counterparts (*P*<0.001). Table S3 presents the baseline characteristics of both men and women, categorized into 4 groups based on their fruit and fruit juice consumption. Differences were found across 4 groups for diabetes diagnosis but not for high blood pressure diagnosis in men. No associations were found across 4 groups for diabetes and high blood pressure diagnosis in women (Table S3). Table S4 displays the baseline CVD risk factors for both men and women.

Kaplan-Meier survival estimates for fruit, fruit juice, and joint fruit and fruit juice consumption and survival are shown in Figure 1. Men and women with high fruit juice consumption had a lower survival rate compared with those with low fruit juice consumption (*P*<0.001; Figure 1B). Those with a combined intake of inadequate fruit and high fruit juice presented with the lowest survival rate, whereas those with adequate fruit combined with low fruit juice consumption were associated with the highest survival (Figure 1C).

Crude and adjusted HR and 95% CI in terms of the association between fruit and fruit juice in relation to survival for men and women are shown in Figure 2. In women, those with inadequate fruit consumption were associated with a higher mortality risk in both crude (HR, 1.10 [95% CI, 1.01–1.91]; *P*=0.03) and adjusted (HR, 1.12 [95% CI, 1.01–1.24]; *P*=0.04) models. In terms of a linear effect (ie, we treated fruit consumption as a continuous variable), fruit consumption was not associated with mortality (adjusted HR, 0.98 [95% CI, 0.94–1.01]; *P*=0.22). Those with high fruit juice consumption were associated with a higher risk of mortality in both crude (HR, 1.74 [95% CI, 1.58–1.91]) and adjusted (HR, 1.26 [95% CI, 1.12–1.41]; *P*<0.001) models compared with those with low fruit juice consumption. This association remained significant when analyzed in a linear effect (adjusted HR, 1.08 [95% CI, 1.04–1.12]; *P*<0.001). Those with high fruit juice consumption with adequate (crude HR, 1.66 [95% CI, 1.47–1.87]; adjusted HR, 1.18 [95% CI, 1.02–1.37]) and inadequate fruit consumption (crude HR, 2.00 [95% CI, 1.74–2.30]; adjusted HR, 1.43 [95% CI, 1.21–1.69]) were associated with a higher risk of mortality. No significant differences were found in the adjusted model for men. In terms of evaluating linear effect for men, higher fruit juice consumption was associated with a higher risk of mortality (adjusted HR, 1.03 [95% CI, 1.01–1.06]; *P*=0.02), but not for fruit consumption (HR, 1.01 [95% CI, 0.98–1.00]; *P*=0.93). No significant interactions between intake and covariates were observed.

There is no evidence that the proportional hazards assumption has been violated, with all *P* values >0.05 (*P* values for variable of fruit, fruit juice, and the joint effect of fruit and fruit were 0.06, 0.81, and 0.27, respectively).

To best avoid reverse causality, we performed a sensitivity analysis of excluding data of the first 2 years of deaths. The results were consistent with our main results. Higher fruit juice consumption was associated with higher risk of mortality in women (adjusted HR, 1.26 [95% CI, 1.12–1.43]; *P*<0.001). Those with high fruit juice consumption with adequate (adjusted HR, 1.20 [95% CI, 1.02–1.40]; *P*=0.02) and inadequate fruit consumption (adjusted HR, 1.43 [95% CI, 1.19–1.71]; *P*<0.001) had a higher risk of mortality. No associations were found in the adjusted model in men.

We also determined the relationships between fruit and fruit juice consumption with the incidence of other disease categories based on *ICD-10-AM* codes. Among 13 code categories, the highest incidence was reported for diseases of the circulatory system (26.5%), expected among people with CVD. This was followed by endocrine, nutrition, and metabolic diseases (13.2%); diseases of the digestive system (12.5%); diseases of the musculoskeletal system and connective tissue (12.4%); and neoplasms (7.5%) (Table S5). Significant associations were obtained for circulatory system, endocrine, nutrition and metabolic disease, and neoplasms in the crude models, but the significances were attenuated after adjusted for confounders (Figure 3). No significant results were found for other *ICD-10-AM* categories in both crude and adjusted models. The sensitivity analysis of excluding the first 2 years of deaths was similar to our main results.

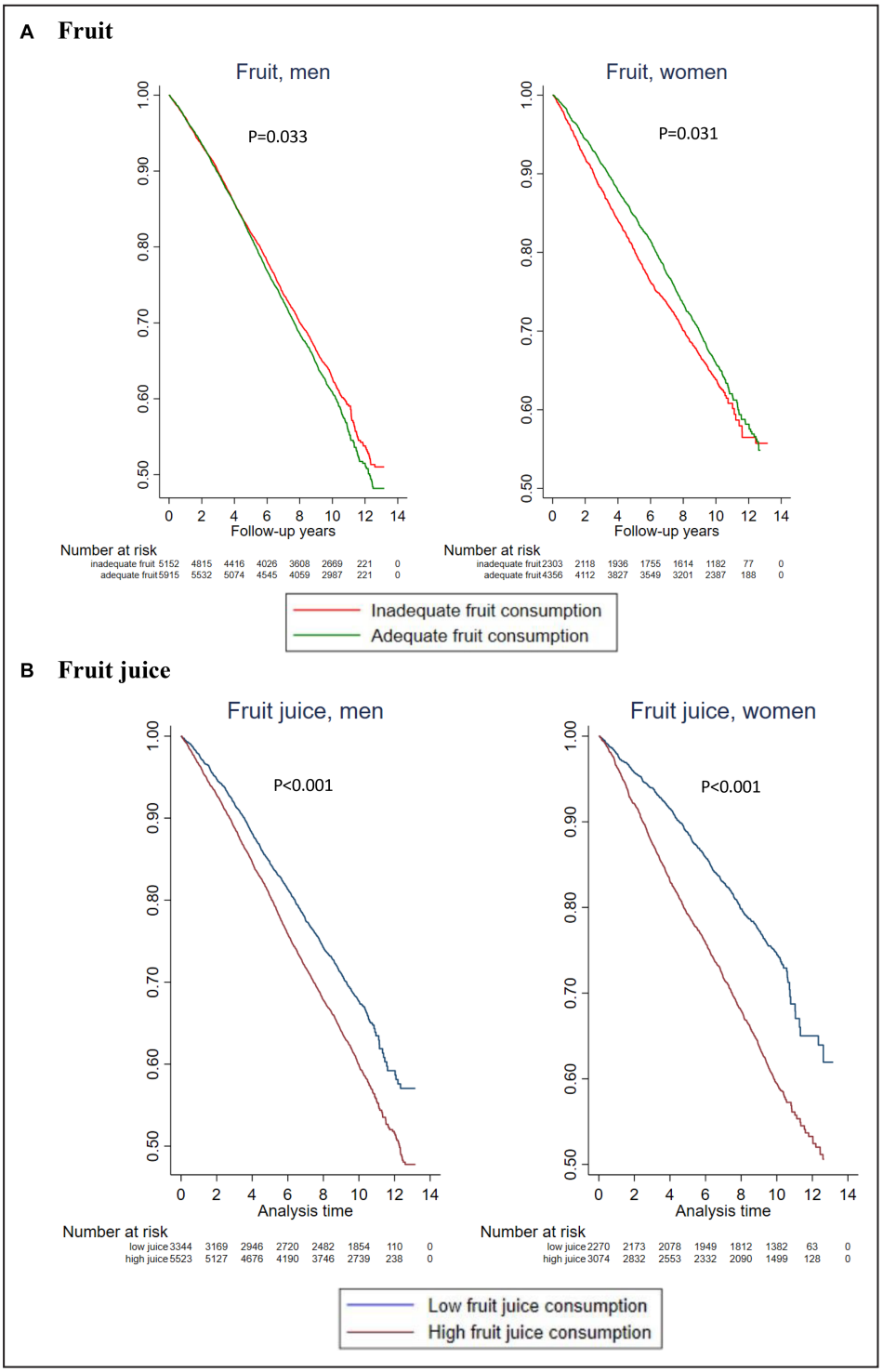

Figure 1. Kaplan-Meier survival estimates for fruit, fruit juice, and joint fruit and fruit juice consumption and survival by men and women (N=18063).
A, Effect of fruit consumption. **B**, Effect of fruit juice consumption. **C**, Joint effect of fruit and fruit juice consumption.

Post Hoc Analysis

We also determined how long-term fruit and fruit juice consumption is associated with mortality. We included men and women who completed dietary questionnaires across both waves of dietary data, yielding a sample of 7236 participants (Figure S1).

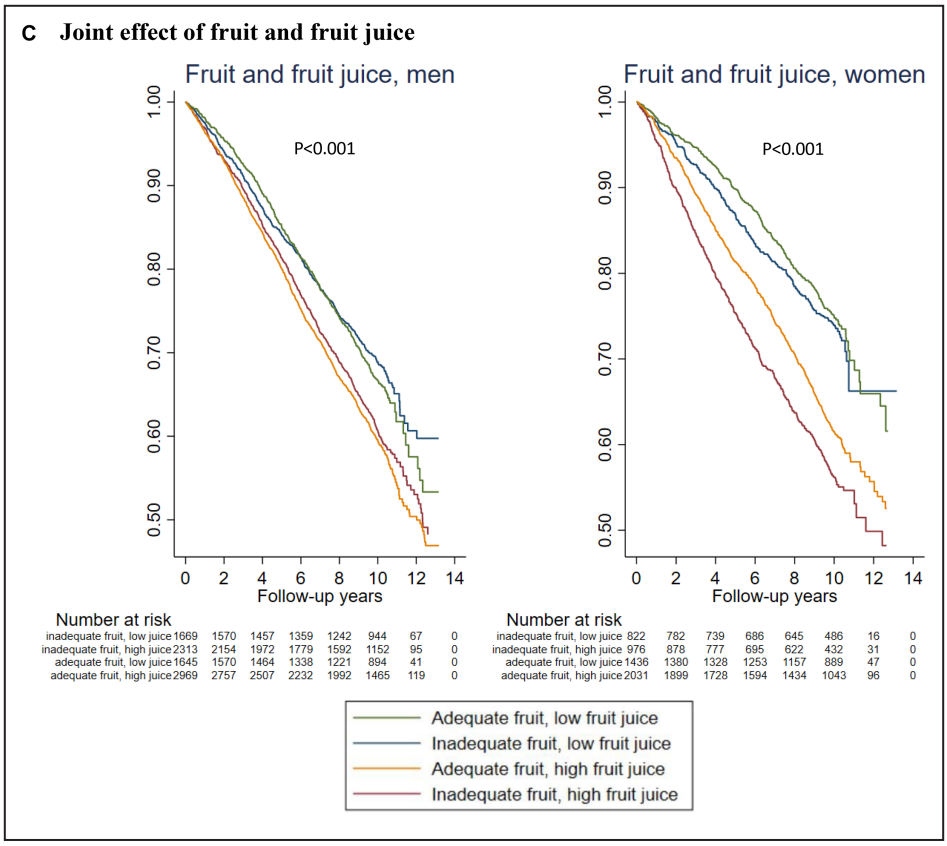

Figure 1. Continued

In men, higher fruit juice consumption was associated with a higher risk of mortality in both crude (HR, 1.94 [95% CI, 1.51–2.48]; *P*<0.001) and adjusted (HR, 1.52 [95% CI, 1.16–1.99]; *P*=0.02) models, but no association when evaluating a linear effect (adjusted HR, 1.03 [95% CI, 0.98–1.09]; *P*=0.23). Compared with men with adequate fruit in addition to low fruit juice consumption, those with high fruit juice combined with adequate fruit intake were associated with a higher mortality (crude HR, 2.15 [95% CI, 1.40–3.29]; adjusted HR, 1.77 [95% CI, 1.12–2.82]). In women, those with long-term inadequate fruit consumption were associated with a higher risk of mortality in the adjusted model (HR, 1.44 [95% CI, 1.01–2.06]; *P*=0.04). Higher fruit juice consumption was associated with a higher risk of mortality when evaluating a linear effect (adjusted HR, 1.10 [95% CI, 1.01–1.19]; *P*=0.03). No significant differences were found in terms of the joint effect of fruit and fruit juice in relation to mortality in the adjusted model (Figure S2).

Similar to the main results, among 13 *ICD-10-AM* categories, the highest incidence was for diseases of the circulatory system (20.2%), indicating the high reoccurrence among people with CVD. This was followed by endocrine, nutrition, and metabolic diseases (16.3%); diseases of digestive system (15.6%); diseases of the musculoskeletal system and connective tissue (13.1%); and neoplasms (8.7%) (Table S6). Aligned with the main results, significant associations were also found for diseases of the circulatory system; endocrine, nutrition, and metabolic diseases; and neoplasms in the crude models, but the significances were attenuated after adjusting for confounders (Figure S3). No significant associations were found for other *ICD-10-AM* categories in both the crude and adjusted models.

DISCUSSION

When following 18 603 men and women with a CVD diagnosis over a 13-year period, we found that those with high fruit juice intake had a higher risk of mortality. This was confirmed in a subset of 7236 participants with confirmed long-term high intake of fruit juice, where 1101 deaths were recorded. Compared with those with adequate fruit intake and low fruit juice intake, women with a high fruit juice intake plus inadequate fruit intake had a 43% greater risk for death. Even when a high fruit juice diet was combined with adequate fruit intake, the risk remained elevated in women (18%), suggesting that the effects of consuming large volumes of fruit juice cannot be easily mitigated. This finding was also

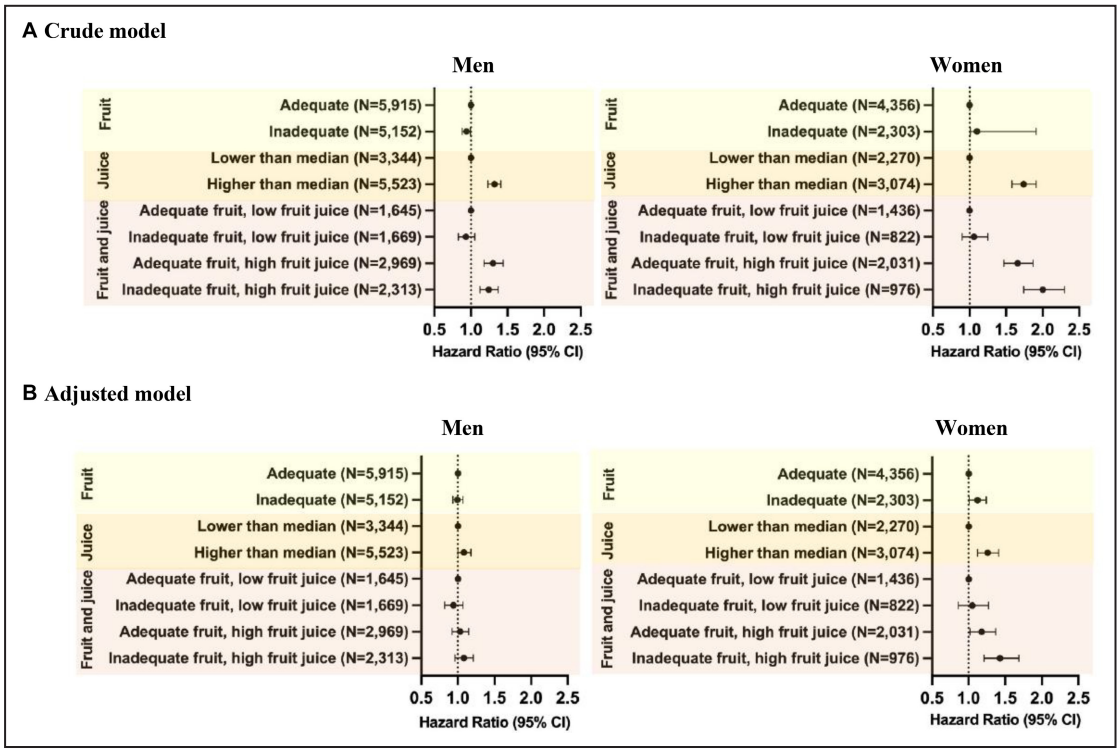

Figure 2. Cox proportional hazard regression models of the association between fruit and fruit juice intake and survival by sex (N=18603).
A, Crude model. **B**, Adjusted model. Hazard ratio in the adjusted model was adjusted for socioeconomic factors, health behaviors, consumption of other food groups, and chronic conditions.

confirmed in men, but only in those with a reported long-term intake of fruit juice.

The effect of fruit juice on health has long been debated, with inconsistent evidence.[3,7,8] The harmful effects of high fruit juice intake predicting all-cause mortality was highlighted from our results, which may be explained by the lower dietary fiber content and the higher energy density when comparing fruit juice to fresh fruit.[7] Fruit juice, in particular 100% fruit juice, has been perceived as an important source of nutrients (eg, vitamin C, carotenoids, and polyphenols) that may benefit health and are therefore widely recognized as a healthier option than sugar-sweetened beverages. Although 100% fruit juice does not contain added sugars, once metabolized, the biological response compared with sugar-sweetened beverages is essentially the same.[23] Juicing removes the insoluble fiber, which usually would help delay the absorption of sugars.[24]

We found a high fruit juice intake to be associated with an increased risk of developing diseases of the cardiovascular system, and endocrine, nutrition and metabolic diseases, although the significance was attenuated after adjusted for confounders. Many studies have examined the role of fruit juice intake in relation to specific disease incidence for primary prevention, with inconsistent results. For example, a recent systematic review of 21 prospective studies and 35 randomized controlled trials concluded that fruit juice was not associated with cardiovascular risk,[7] whereas a meta-analysis of 17 prospective cohort studies highlighted that each additional daily serving of fruit juices was associated with 7% greater risk of type 2 diabetes.[25]

The evidence for secondary prevention is limited, although cardiovascular event recurrences are common, with a 41.5% recurrence rate being reported in a Finnish study, and 47% to 54% were reported in a US study.[26,27] Comorbidities together with CVD are also common. People with CVD often live with chronic conditions such as diabetes and chronic kidney disease.[28] Because further research is needed on the role of fruit and fruit juice for secondary prevention, we focused on this cohort.

We found that adequate fruit intake does not mitigate the adverse effects of fruit juice on mortality, particularly in women. Given that no other studies have explored the joint effects of fruit and fruit juice on health, we were unable to compare our findings. However, our results emphasized the importance of portion control in fruit juice consumption, which is aligned with some previous studies and dietary guidance in Australia. For instance, 1 study reported that <5 oz (approximately 210 mL) of fruit juice per week was associated with a

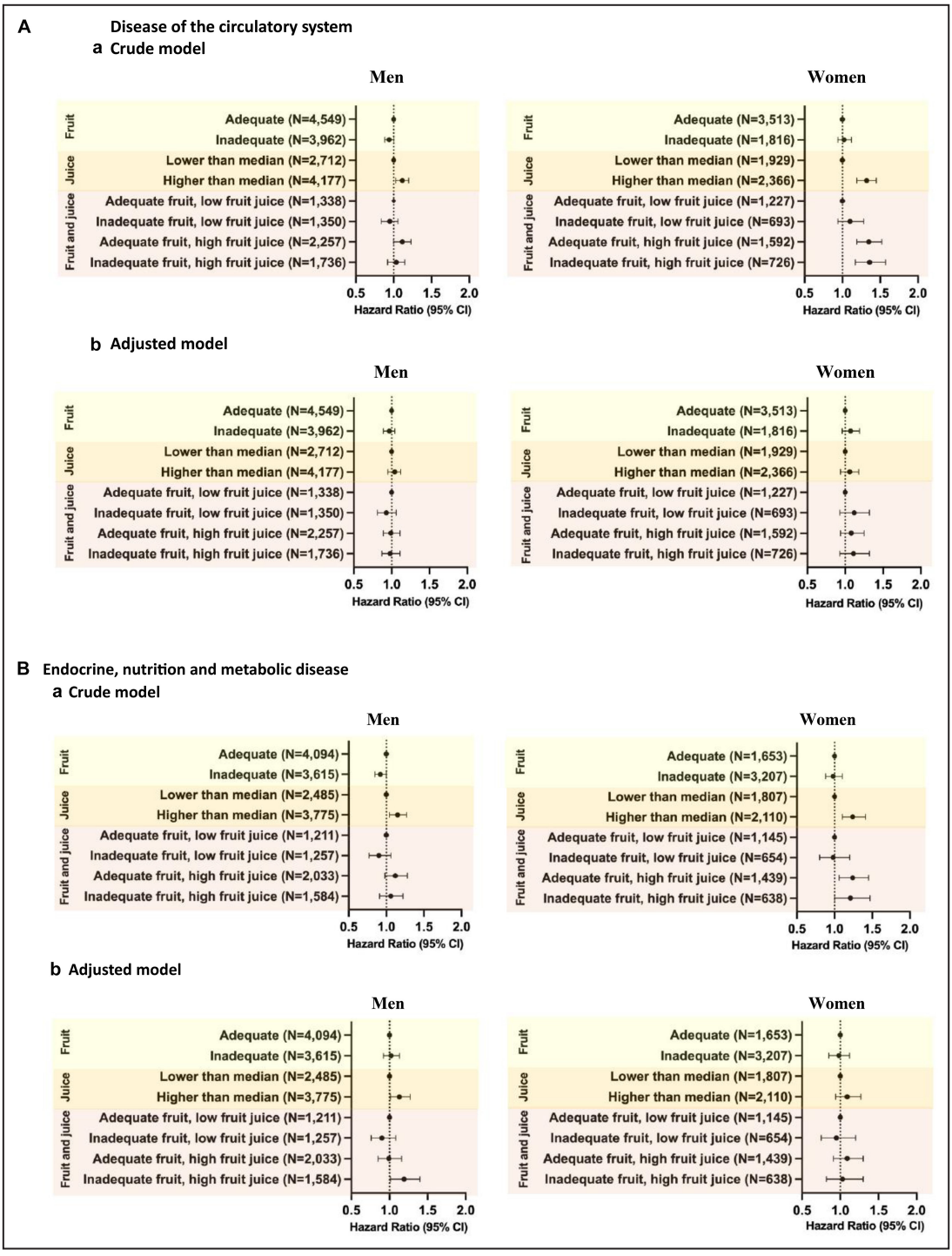

Figure 3. Cox proportional hazard regression models of the association between fruit and fruit juice intake and incidence of disease categories based on *International Classification of Diseases, Tenth Revision, Australian Modification* codes (N=18603).

A, Diseases of the circulatory system. **B**, Endocrine, nutrition, and metabolic diseases. **C**, Neoplasms. Hazard ratio in the adjusted model was adjusted for socioeconomic factors, health behaviors, consumption of other food groups, and chronic conditions.

17% lower risk of CVD and a 24% lower risk of stroke.[29] Daily consumption of 250 mL or more of total fruit juice increased overall mortality by 28% and CVD mortality by 48%.[5] Each additional 12 oz serving (approximately 350 mL) of fruit juice consumption increased the mortality risk by 24%.[4]

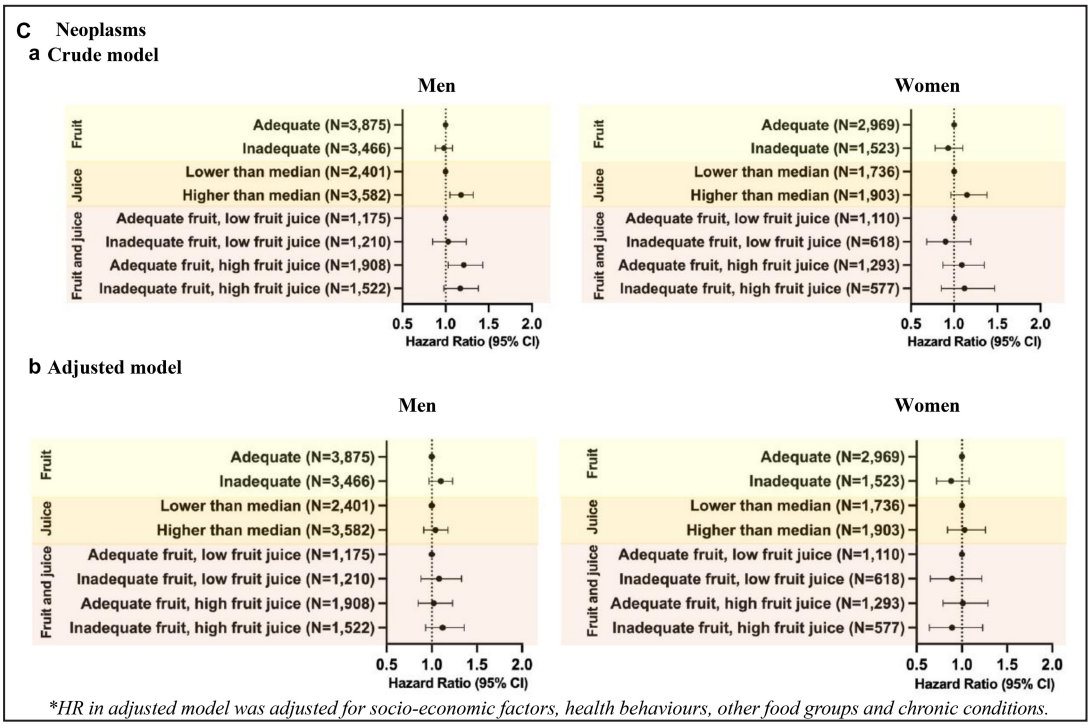

Figure 3. **Continued**

Our focus on sex differences in terms of the effect of high fruit juice consumption in relation to mortality is important. Many studies have pointed to differences in dietary patterns and behaviors impacting health outcomes,[11] but few studies have specifically examined sex differences in fruit and fruit juice intake to evaluate its effects on mortality and disease incidence. Our findings align with a recent call from the Australian Sex and Gender Sensitive Research Group that implementing sex analysis in health and medical research can provide a better understanding on how sex influences the manifestation of certain diseases, encourages equity, and saves lives.[30]

The strengths of our study are that it involved a large population sample followed over a long period of time that allow us to understand effects of fruit and fruit juice intake on health outcomes by different sexes. Long-term dietary behavior has also been tracked, which helped us to further understand the effect of long-term fruit and fruit juice consumption. More importantly, we generated new evidence to understand the joint effects of fruit and fruit juice intake on mortality.

The generalizability needs to be noted in that the 45 and Up Study sample skews toward higher income groups, as well as oversampling of people aged ≥80 years and residents of rural and remote areas.[31] Limitations include the use of self-reported data, which may potentially introduce measurement bias and not being able to know the quality of the fruit and fruit juice data. First, in the questionnaire, a serving of fruit was identified as 1 medium piece or 2 small pieces or 1 cup of diced or canned fruit pieces. Canned fruit may include added sugar or juice, both of which are higher in sugar than fresh whole fruit. Similarly, it is unknown if the data for fruit juice were 100% fruit juice or sugar-sweetened fruit juice. This limitation prevents us from making further assessment of the dietary intake. Second, although it would be interesting to examine the role of different types of fruit juice consumption in relation to mortality, this was not defined in the questionnaire. We can only estimate fruit juice consumption as glasses, without knowing the exact volume, thereby not allowing us to perform a dose-specific analysis. A glass may be interpreted as 250 mL, which is double the amount recommended in the Australian Guide to Healthy Eating (125 mL). Third, a short dietary questionnaire does not capture all food and beverages. Some dietary confounders, such as dried fruit and fast or processed food consumption, were not able to be included in the analysis because of data availability. Fourth, it is plausible that individuals may alter their fruit or fruit juice consumption between the 2 time points, for instance, transitioning from adequate to inadequate intake or vice versa. However, we did not include these participants in the analysis, because our aim to preform longitudinal analysis was to track long-term behavior of fruit and fruit juice consumption. This approach resulted in a reduced sample size, which may have impacted statistical power. In addition, by only including individuals who had 2 measurements in this analysis, there is a possibility of introducing selection

bias. Specifically, it is likely that only relatively healthy individuals completed both the baseline and follow-up questionnaires. For example, of the individuals who completed only the baseline survey, 60.8% were diagnosed with high blood pressure and 67% were diagnosed with diabetes; whereas among those who completed both the baseline and follow-up surveys, 39.2% were diagnosed with high blood pressure and 33% were diagnosed with diabetes at baseline. Fifth, although the impact of CVD treatments (eg, antihypertensive medication) during the follow-up period has not been included and may impact on study outcomes, baseline variable adjustments have been made in the Cox proportional hazard regression models. Last, although it would be worth testing if other causes of death could be competing risks for CVD events and death, it was not feasible to perform due to the complexity of the data (ie, each participant can have up to 20 causes of death and up to 55 disease diagnoses).

CONCLUSIONS

Inadequate fruit intake increased the risk of all-cause deaths by 12%, and a high intake of fruit juice increased the risk of all-cause deaths by 26% in women with existing CVD. In those with a high fruit juice plus adequate fruit intake, the risk for death remained elevated at 18%, whereas a combination of juice with inadequate fruit intake led to a 43% increase in all-cause deaths in women with CVD. This finding was confirmed in men but only in those with long-term fruit juice intake.

Our findings suggest that fruit juice intake should be limited for secondary prevention of CVD, with dietary advice focused on adequate whole fruit intake. Our results need to be confirmed in other population-based studies to allow sufficient consistent evidence for policy solutions in promoting healthy eating.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S6
Figures S1–S3

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