Cardiovascular Health Effects of 100% Fruit Juice Versus Whole Fruit in Postmenopausal Women: Results from the Women's Health Initiative

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A thesis
submitted in partial fulfillment of the
requirements for the degree of

Master of Public Health

University of Washington

2016

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Program Authorized to Offer Degree:

Epidemiology

University of Washington

Abstract

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Introduction

We investigated whether 100% fruit juice and whole fruit were independently related to incident hypertension or incident type 2 diabetes.

Methods

We included women 50-79 years old enrolled in the Women's Health Initiative. The risk of incident hypertension was analyzed in 80,539 participants and risk of incident diabetes in 114,219 participants. One hundred percent fruit juice and whole fruit intake were assessed by baseline food frequency questionnaire. Standardized questionnaires assessed medical history and other characteristics at baseline and every 6-12 months during follow-up. Cox regression, adjusted for demographic, socioeconomic, behavioral, and dietary variables (including total energy intake) was used to estimate hazard ratios (HR) for the associations between 100% fruit juice and whole fruit consumption and incident hypertension and diabetes during a mean of 7.8 years of follow-up.

Results

In multivariable analyses, there was no association between 100% fruit juice consumption and incident hypertension (highest vs. lowest quintile, HR 1.00, 95% CI 0.97-1.03) or incident diabetes (HR 0.98, 95% CI 0.92-1.04). There was also no association between whole fruit consumption and incident hypertension (HR 1.20, 95% CI 0.98-1.05) or incident diabetes (HR 1.03, 95% CI 0.96-1.10).

Conclusion

Greater consumption of 100% fruit juice or whole fruit was not associated with risk of incident hypertension or diabetes among postmenopausal US women.

Introduction

One hundred percent fruit juice is rich in nutrients like potassium and polyphenols, but it is also high in naturally occurring sugars and may be associated with adverse cardiometabolic health effects.[1,2] Experts disagree on how 100% fruit juice should be treated in healthy beverage policies, including taxes on sugary beverages, food warning labels, and traffic light food labeling programs.[3] It is a priority to determine where 100% fruit juice falls in the spectrum of healthy beverage options.

One hundred percent fruit juice may be associated with adverse cardiovascular health effects, such as hypertension and diabetes, through several possible biological mechanisms. (1) One hundred percent fruit juice may contribute excess calories and thus be associated with hypertension and diabetes through increased energy intake and weight gain.[4] (2) One hundred percent fruit juices have a higher glycemic index than the whole fruits they are extracted from,[5] and consumption of large portions of 100% fruit juice may cause a high postprandial insulin response that predisposes to diabetes through a mechanism independent of weight gain.[6] A high postprandial insulin response may cause an increased anabolic response to eating and decreased free fatty acid synthesis, which causes the blood glucose concentration to quickly fall and triggers a hormonal state resembling fasting that is accompanied by hunger.[6] (3) Metabolism of the fructose in 100% fruit juice may cause increased uric acid production, leading to both elevated blood pressure and insulin resistance.[7,8]

Despite the theoretical impacts of a diet high in 100% fruit juice on cardiovascular health, meta-analyses have found little evidence that 100% fruit juice consumption is associated with

hypertension or diabetes. Liu et al. has conducted the only meta-analysis to date of 100% fruit juice consumption and incident hypertension, including 8 small, randomized controlled trials (RCTs; n = 236 individual adult participants). Liu et al. found that the mean difference in systolic blood pressure between subjects who consumed 100% fruit juice compared to subjects who consumed the comparator beverages was -2.03 mmHg (95% CI: -4.47 mmHg, 0.41 mmHg).[9] For diastolic blood pressure this difference was -2.07 mmHg (95% CI: -3.75 mmHg, -0.39 mmHg). Limitations of the meta-analysis by Liu et al.'s are that the RCTs included had short follow-up durations (5-12 weeks), participants in some RCTs had baseline hypertension and other chronic diseases that affect blood pressure, and 100% fruit juice was compared to a range of beverages including water, sugar-sweetened beverages, and 100% grapefruit juice.

Two meta-analyses of the association between 100% fruit juice and incident diabetes found little evidence of an association between 100% fruit juice and diabetes in adults.[10,11] Xi et al. analyzed 3 prospective cohort studies (n = 137,663 individual adult participants) and compared the highest to lowest quantile of 100% fruit juice consumption.[10] Participants in the highest quantile consumed $\geq$ 1 serving per day (/d) of 100% fruit juice, compared to < 1 serving/week in the lowest quantile (exact serving sizes not reported). Xi et al. found a pooled relative risk (RR) of incident diabetes of 1.03 (95% CI: 0.91-1.18). Imamura et al. analyzed 14 prospective cohort studies (n = 440,937 individual adults) and found that the RR of objectively ascertained incident diabetes per 1 serving/day increment of 100% fruit juice consumed was 0.98 (95% CI: 0.86-1.11).[11] Serving sizes were 8-12 ounces (oz.)/d. None of the studies included in either meta-analysis by Imamura et al. or Xi et al. examined a population of postmenopausal women, who are at higher risk of diabetes compared to premenopausal women because (1) an increase in the

concentration of blood androgens may worsen glucose control, (2) visceral fat deposition increases, and (3) resting energy expenditure slows, which predisposes to weight gain.[12,13,14]

The question of whether, and how much, 100% fruit juice adults should drink is important to consumers and policy makers. Additional studies with longer durations are needed. We undertook this secondary analysis of the Women's Health Initiative (WHI), a large and diverse sample of postmenopausal American women, to determine if fruit juice consumption is associated with incident hypertension or diabetes.

Methods

Study Design and Population:

The design and methods of the WHI have been described in detail elsewhere.[15] Briefly, the WHI enrolled 161,808 post-menopausal women ages 50-79 years between 1993-1998 into the WHI Observational Study (OS) and 3 randomized controlled trials. We analyzed participants in the OS (n = 93,679) and control arm of the Dietary Modification Clinical Trial (DM CT, n = 29,294). Participants in the control arm of the DM CT did not receive the dietary intervention of a low-fat diet.

Our inclusion criterion was baseline food frequency questionnaire (FFQ) completion. Our exclusion criteria were (1) Energy intake outliers on baseline FFQ (defined as $\leq$ 600 kcal/day or $\geq$ 5000 kcal/day),[16] (2a) baseline self-reported past or current hypertension for the analyses of incident hypertension, (2b) baseline self-reported past or current diabetes (not counting

gestational diabetes) for the analyses of incident diabetes, and (3) missing answers to both 100% fruit juice questions on the FFQ.

3,614 participants were excluded for reporting extreme energy intake on the baseline FFQ, and 174 participants were excluded for not reporting baseline 100% fruit juice intake (Supplemental Table A and B). 38,646 participants reported a history of hypertension and were excluded from the analysis of incident hypertension, but retained in the analysis of incident diabetes. 4,966 participants reported a history of diabetes and were excluded from the analysis of incident diabetes, but retained in the analysis of incident hypertension. This left 80,539 participants in the analysis of incident hypertension and 114,219 participants in the analysis of incident diabetes.

Exposure Assessment

The primary exposure of interest was 100% fruit juice consumption, as measured by a semi-quantitative FFQ designed for the WHI.[17] FFQs were administered at baseline to all participants, and at year 3 to all OS participants, and to DM CT participants in a systematic subsampling throughout follow-up. The FFQ contained 2 separate items asking about (1) 100% orange and grapefruit juices, and (2) all other 100% fruit juice types. Participants were asked to specify their usual serving size as small (3 oz.), medium (6 oz.), or large (12 oz.), and to indicate the frequency of intake as 1 of 9 response options, ranging from "never or < 1 serving per month" to "2+ servings daily." Serving size was multiplied by frequency to obtain the daily estimate of 100% fruit juice intake, and was analyzed as the mean oz./d of 100% fruit juice consumed. To increase statistical power and reduce measurement error by constraining outliers, we analyzed quintiles of daily 100% fruit juice intake.

Because the relationship between 100% fruit juice and chronic diseases such as hypertension and diabetes may be confounded by a prudent eating pattern (defined by high intake of whole grains, fruit, vegetables, fish, lean protein, and low intake of saturated fat and sugary foods and beverages), we also analyzed whole fruit as a comparator exposure.[16,18] We standardized intake of 100% fruit juice intake and whole fruit to 2000 kilocalories (kcal)/d using the residual method to control for the fact that individuals who consume more calories often report consuming more of individual food groups, including 100% fruit juice and whole fruit.[19]

Covariate Assessment

Baseline data related to demographic characteristics, medical history, and health behaviors were collected at baseline using standardized questionnaires. The validity of these baseline measures has been described in detail elsewhere.[20] Physical measurements including body weight, height, and blood pressure were measured by trained and certified study personnel at baseline using standardized protocols in all WHI participants.

Outcome Assessment

Our primary outcomes were self-reported incident hypertension or diabetes. Standardized medical history questionnaires asking about new diagnoses or treatment of hypertension and diabetes were completed every 6 months by CT participants, and annually by OS participants until the conclusion of the DM CT and OS studies in March 2005. Participants were considered to have incident hypertension or diabetes if they initiated medication to treat hypertension ("pills for high blood pressure") or diabetes ("pills or insulin shots for diabetes"). Data from a WHI data confirmation study showed that incident diabetes as measured by these questions was consistent

with medication inventories.[21] Our outcome measure of incident hypertension was based on self-report, and has been used in other WHI analyses.[22,23]

Statistical Analysis

Quintiles of baseline 100% fruit juice consumption were evaluated as ordinal variables to assess trend using the log-rank test. We used Cox proportional hazards to estimate the multivariable-adjusted hazard ratio (HR) of incident hypertension and diabetes. Time at risk was calculated from baseline to the date of first diagnosis reported on follow-up questionnaire or among those disease-free, until the participants' last follow-up visit (April 2004 - March 2005). The proportional-hazards assumption was not rejected based on Schoenfeld residuals.

Variables tested as potential confounders were age (years), education level (4 levels), race/ethnicity (Asian/Pacific, Black, Hispanic/Latino, White), smoking status (never, past, current), number of alcoholic drinks per week, leisure-time physical activity (metabolic equivalent [MET]-hours/week), body mass index (BMI, measured continuously), mean daily sodium intake (mg/d), total energy intake (kcal/d), mean daily sodium intake (mg/d), total energy intake (kcal/d), diet quality as measured by the 2005 Healthy Eating (HEI) index, WHI study arm (OS or DM CT control-arm), and use of postmenopausal hormone replacement therapy (never, past, current). The number of alcoholic drinks/week and mean daily sodium intake were associated with < 10% change in the regression coefficient for our exposure variable, 100% fruit juice consumption, and were dropped from the final regression models for parsimony. All analyses were conducted with STATA (version 14, StataCorpLP, College Station, Texas). A two-sided p-value < 0.05 was considered statistically significant for all analyses.

We performed several sensitivity analyses. We examined the influence of (1) stratifying by categories of age (< 50-59, 60-69, 70-79+ years); (2) stratifying by study arm; (3) using cutpoints defined by Borgi et al.[24] to categorize the exposure (≤ 4 servings/week; 5-6 servings/week; 1 serving/d; 2-3 servings/d; ≥ 4 servings/d), and (4) change analysis as described Smith et al.,[25] which measured change in 100% fruit juice consumption and change in incident hypertension and diabetes over the same 3-year time period.

Ethics

The WHI study protocol was approved by Institutional Review Boards (IRBs) at each participating institution, and all participants provided written informed consent. Additionally, local IRB approval was obtained for use of WHI data at the University of Washington. The ClinicalTrials.gov Identifier is NCT00000611.

Results

The baseline characteristics of the 80,539 participants analyzed for incident hypertension and 114,219 participants analyzed for incident diabetes were similar across quintiles of 100% fruit juice consumption (Tables 1A & 1B). Participants in the highest quintile of 100% fruit juice consumption (range 9.5-36.8 oz./d of 100% fruit juice) were slightly more likely to be older, have a normal BMI (18.5-25.0 kg/m^2), be African American, have higher educational attainment, and have a higher 2005 HEI diet quality score.

Greater 100% fruit juice consumption was not associated with incident hypertension (Table 2) or diabetes (Table 3). Among 80,539 participants free of hypertension, 26,108 new cases occurred

during 439,626 person-years of follow-up. Among 114,219 participants free of diabetes, 11,488 new cases occurred during 837,733 person-years of follow-up. The mean individual follow-up time for both groups was 7.8 years. In multivariable-adjusted analyses comparing highest to lowest quintiles, greater 100% fruit juice intake was not associated with incident hypertension (HR 1.00, 95% CI 0.97-1.03) or diabetes (HR 0.98, 95% CI 0.92-1.04). Relationships were similar in the univariate and the multivariable-adjusted models.

Greater whole fruit consumption was also not associated with incident hypertension (Table 4) or diabetes (Table 5). In multivariable-adjusted analyses comparing the highest to lowest quintiles, greater whole fruit intake was not associated with risk of hypertension (HR 1.02, 95% CI 0.98-1.05) or diabetes (HR 1.03, 95% CI 0.96-1.10), and associations were similar in univariate and multivariable-adjusted models.

Sensitivity analyses of baseline age, study arm, or change analysis did not show an association between either the exposure of 100% fruit juice or whole fruit and either outcome of incident hypertension or diabetes (Table 6). Our sensitivity analysis categorizing the exposures of 100% fruit juice and whole fruit using cut-points based on serving sizes showed an increase in hypertension risk associated with consuming $\geq$ 4 servings/d of 100% fruit juice (HR 1.29, 95% CI 1.06-1.57), but the trend was not significant (P for trend = 0.21; Table 7A). Categorizing the exposures using cut-points otherwise yielded null associations for trend (Tables 7A & 7B).

Discussion

Our objective was to investigate whether 100% fruit juice consumption was associated with incident hypertension and diabetes, adjusting for total energy intake and other confounding factors. We compared consumption of 100% fruit juice to whole fruit. In our primary analysis, we found no evidence that 100% fruit juice or whole fruit was associated with incident hypertension or diabetes. In sensitivity analyses, consuming $\geq$ 4 servings/d of 100% fruit juice was associated with an increase in hypertension risk, but the trend of increasing 100% fruit juice serving size and hypertension risk was not significant. All other sensitivity analyses yielded null associations.

To our knowledge, this is the first longitudinal analysis of 100% fruit juice intake and hypertension risk. Previous cohort studies have examined the association of whole fruit, but not 100% fruit juice, and hypertension. Borgi and colleagues analyzed 187,453 adults in the Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-Up Study for a mean follow-up time of 15.7 years.[24] They compared participants who consumed $\geq$ 4 servings/d of whole fruit to participants who consumed $\leq$ 4 servings/week of whole fruit, and found a multivariable adjusted HR of 0.92 (95% CI 0.87-0.97) for incident hypertension. When we analyzed 100% fruit juice and whole fruit dietary exposures using the same categories as Borgi et al., we found that whole fruit was associated with a similar but non-significant decreased risk of hypertension (HR 0.94; 95% CI 0.83-1.05), and found that 100% fruit juice was associated with an increased risk of hypertension (HR 1.29; 95% CI 1.06-1.57). In sensitivity analyses using the cut-points of serving sizes defined by Borgi et al.,[24] the trend of increasing serving size and hypertension risk was not significant for either 100% fruit juice or whole fruit.

Our findings that postmenopausal women in the WHI in the highest versus lowest quintiles of 100% fruit juice and whole fruit consumption were not at increased risk for diabetes are similar to findings from other cohort studies.[10,11,28] Muraki and colleagues analyzed 187,382 adults in the same 3 cohort studies as Borgi and colleagues over a mean follow-up time of 18.5 years. Muraki et al. analyzed the associations of changes in consumption over 4-year time periods of (1) 100% fruit juice, and (2) whole fruit, with diabetes risk over the same 4-year time periods.[26] In multivariable analyses, each 3-serving/week increment in 100% fruit juice consumption was associated with an 8% (95% CI 1.05, 1.11) increased risk of incident diabetes. Each 3-serving/week increment in whole fruit consumption was associated with a decreased risk of incident diabetes (HR=0.98, 95% CI 0.96, 0.99). Though statistically significant, the HRs found by Muraki et al. are close to a null HR of 1.0 and rule out a large impact.

Our findings are similar to the results of other investigators,[10,11,24,28] and are relevant to US dietary policy. The 2015-2020 US Dietary Guidelines for Americans (DGA)[27] and the Robert Wood Johnson Foundation (RWJF)[28] recommend that adults limit 100% fruit juice to one 8-oz serving/d, given the high prevalence of overweight and obesity in the US. Guidelines from both groups emphasize that consuming water and whole fruit is preferred to 100% fruit juice, since 100% fruit juice contains less dietary fiber than whole fruit, and when consumed in excess, 100% fruit juice may contribute extra calories to Americans' diets. Some experts have argued that, because of the high prevalence of overweight/obesity in the US, diet policies should recommend that adults do not drink any 100% fruit juice, and instead consume only whole fruit.[29] Our findings showed that postmenopausal women who consumed an average of 9.5 oz./d of 100% fruit juice (highest quintile) compared to $\leq$ 1.0 oz./d of 100% fruit juice (lowest

quintile) were not at increased risk of hypertension or diabetes, and support existing policy recommendations of the DGA and RWJF.

This analysis has limitations. Exposure misclassification may be present from participants misunderstanding questions on the FFQ about 100% fruit juice versus fruit drinks like Tang®, which could bias associations away from the null. Despite adjusting for diet quality, physical activity, socio-economic position, and other covariates, there may be residual unmeasured confounding of healthy behaviors and 100% fruit juice consumption, which could bias our associations towards the null.[16] Mean fruit juice consumption among WHI participants was relatively low, reducing power to examine whether higher levels of consumption are more strongly associated with risk of diabetes or hypertension. Finally, our outcome measure of incident hypertension was based on self-report, and has been used in other WHI analyses but has not been objectively validated.

Conclusion

In this secondary analysis of postmenopausal women in the WHI, 100% fruit juice was not associated with incident hypertension or diabetes in postmenopausal women. Our findings suggest that evidence linking 100% fruit juice and adverse cardiometabolic outcomes is markedly weaker compared to evidence linking sugar-sweetened beverages and adverse cardiometabolic outcomes.[7] Additional experimental studies with follow-up durations of several years are needed to confirm that 100% fruit juice is not associated with risk of hypertension or diabetes. Our findings compliment previous studies and suggest that consuming 100% fruit juice

in the quantities recommended by the DGA and RWJF, $\leq$ 8 oz/d, does not increase risk of hypertension or diabetes.

Table 1A. Baseline Characteristics According to 100% Fruit Juice Consumption of 80,539 Postmenopausal US Women Analyzed for Hypertension Risk					
	Quintiles of 100% Fruit Juice Consumption				
	I	**II**	**III**	**IV**	**V**
Range oz./d of 100% fruit juice	**0-1.0**	**1.0-2.1**	**2.2-4.0**	**4.1-6.6**	**6.7-36.8**
Mean oz. /d of 100% fruit juice	**0.5 ± 0.4**	**1. 5 ± 0.3**	**3.1 ± 0.5**	**5.3 ± 0.8**	**9.5 ± 3.7**
N	**16,108**	**16,108**	**16,108**	**16,108**	**16,107**
Age, years					
50-59	40.5%	39.5%	35.5%	33.6%	36.1%
60-69	43.5%	42.8%	43.9%	44.4%	42.2%
70-79	16.0%	17.7%	20.6%	22.0%	21.5%
BMI category					
Normal (18.5 - 24.9 kg/m^2)	35.8%	41.4%	42.4%	43.6%	47.8%
Overweight (25.0 - 29.9 kg/m^2)	35.2%	35.5%	34.2%	34.9%	32.6%
Obese (> 30.0 kg/m^2)	27.8%	22.0%	22.1%	20.5%	18.3%
Blood pressure, mmHg					
Systolic	122.4 ± 15.6	121.9 ± 15.9	122.6 ± 15.8	122.9 ± 15.9	122.5 ± 16.1
Diastolic	73.5 ± 8.6	73.4 ± 8.6	73.4 ± 8.7	73.5 ± 8.6	73.3 ± 8.7
Race/Ethnicity					
Asian/Pacific	2.0%	3.3%	2.6%	2.6%	2.4%
Black	3.8%	5.1%	5.7%	6.6%	7.5%
Hispanic/Latino	3.7%	4.6%	4.0%	3.5%	3.3%
White	89.2%	85.2%	86.3%	86.0%	85.5%
Education					
< High school diploma	4.3%	3.2%	2.8%	2.5%	2.4%
High school diploma	16.7%	16.7%	15.6%	15.2%	12.7%
School after high school	37.5%	36.5%	37.1%	35.9%	34.2%
College degree or higher	41.6%	42.0%	43.3%	45.3%	49.6%
Smoking					
Never	51.1%	50.9%	51.5%	51.8%	51.2%
Past	41.9%	41.8%	41.6%	41.3%	42.0%
Current	7.0%	7.3%	6.9%	6.9%	6.8%
Use of postmenopausal hormones					
Never	43.5%	44.3%	44.3%	44.2%	44.8%
Past	16.2%	16.2%	16.5%	16.1%	15.2%
Current	40.4%	39.5%	39.2%	39.7%	40.0%
Recreational physical activity level, MET-hours/week	11.9 ± 13.4	11.9 ± 13.6	12.0 ± 13.5	12.0 ± 13.6	12.0 ± 13.5
Energy intake, Kcal/day	1931 ± 630	1350 ± 559	1560 ± 571	1650 ± 601	1610 ± 592
2005 HEI diet quality score	64.9 ± 11.8	67.3 ± 11.0	68.1 ± 10.3	69.2 ± 9.8	71.0 ± 9.0
All characteristics were assessed at baseline (1993-1998). Values are mean ± SD (continuous variables) or percent (categorical variables). Not all categories sum to 100% due to rounding of data within some categories. Servings/d of 100% fruit juice are adjusted for energy using the residual method, and standardized to 2000 kcal/d.					

Table 1B. Baseline Characteristics According to 100% Fruit Juice Consumption of 114,219 Postmenopausal US Women Analyzed for Diabetes Risk					
	Quintiles of 100% Fruit Juice Consumption				
	I	**II**	**III**	**IV**	**V**
Range oz./d of 100% fruit juice	**0-1.0**	**1.1-2.2**	**2.3-4.0**	**4.1-6.6**	**6.7-36.8**
Mean oz. /d of 100% fruit juice	**0.5 ± 0.4**	**1.6 ± 0.4**	**3.2 ± 0.54**	**5.5 ± 0.8**	**9.7 ± 3.8**
N	**22,844**	**22,844**	**22,844**	**22,844**	**22,843**
Age, years					
50-59	21.8%	20.4%	19.0%	17.8%	18.9%
60-69	44.6%	44.2%	44.8%	45.5%	43.6%
70-79	18.1%	20.3%	23.6%	24.6%	24.4%
BMI category					
Normal (18.5 - 24.9 kg/m^2)	31.9%	36.6%	37.8%	38.7%	41.9%
Overweight (25.0 - 29.9 kg/m^2)	34.8%	35.3%	34.9%	35.0%	33.7%
Obese (> 30.0 kg/m^2)	32.4%	27.1%	26.2%	25.4%	23.4%
Blood pressure, mmHg					
Systolic	126.1 ± 17.3	126.0 ± 17.6	127.0 ± 17.6	127.4 ± 17.7	127.4 ± 18.1
Diastolic	75.0 ± 9.1	74.9 ± 9.1	75.0 ± 9.3	75.2 ± 9.2	75.1 ± 9.4
Race/Ethnicity					
Asian/Pacific	2.0%	3.3%	2.7%	2.5%	2.6%
Black	4.6%	6.8%	7.4%	8.8%	10.6%
Hispanic/Latino	3.4%	4.3%	3.7%	3.1%	3.2%
White	88.4%	88.9%	84.7%	84.3%	82.2%
Education					
< High school diploma	4.6%	5.3%	4.6%	4.1%	4.1%
High school diploma	17.6%	17.3%	16.8%	15.8%	13.7%
School after high school	38.0%	37.6%	37.9%	36.6%	35.5%
College degree or higher	39.8%	39.8%	40.8%	43.4%	46.7%
Smoking					
Never	51.3%	51.2%	51.9%	51.3%	51.7%
Past	41.8%	41.7%	41.0%	41.5%	41.4%
Current	6.9%	7.1%	7.1%	7.2%	6.9%
Use of postmenopausal hormones					
Never	43.4%	44.3%	44.8%	44.1%	44.6%
Past	16.2%	16.2%	16.2%	16.1%	15.7%
Current	40.4%	39.5%	39.0%	39.7%	39.7%
Recreational physical activity level, MET-hours/week	11.9 ± 13.4	12.0 ±13.5	12.0 ± 13.6	11.9 ± 13.5	12.0 ± 13.6
Energy intake, Kcal/day	1921 ± 629	1362 ± 575	1556 ± 576	1670 ± 602	1610 ± 615
2005 HEI diet quality score	64.8 ± 11.8	67.0 ± 11.0	68.0 ± 10.3	69.0 ± 9.8	70.9 ± 9.2
All characteristics were assessed at baseline (1993-1998). Values are mean ± SD (continuous variables) or percent (categorical variables). Not all categories sum to 100% due to rounding of data within some categories. Servings/d of 100% fruit juice are adjusted for energy using the residual method, and standardized to 2000 kcal/d.					

Table 2. Incidence of Hypertension Between 1993 and 2005 According to 100% Fruit Juice Consumption in 80,539 Postmenopausal US Women

	Quintiles of 100% Fruit Juice Consumption					P for Trend
	I	II	III	IV	V	
Range oz./d of 100% fruit juice	**0-1.0**	**1.0-2.1**	**2.2-4.0**	**4.1-6.6**	**6.7-36.8**	
Person-years of follow-up	91,441	92,801	91,708	91,943	91,254	
Number of incident cases	9328	9206	9174	9217	9277	
Incidence rate, per 1000 person-years	102	99.2	100	100	102	
Univariate hazard ratio (95% CI)	1.0 (ref)	0.97 (0.94-1.00)	0.98 (0.95-1.01)	0.98 (0.95-1.00)	1.00 (0.97-1.02)	0.19
Multivariable-adjusted* hazard ratio (95% CI)	1.0 (ref)	0.97 (0.94-1.00)	0.98 (0.95-1.01)	0.98 (0.94-1.00)	1.00 (0.97-1.03)	0.34

*Adjusted for age, education level, race/ethnicity, smoking status, physical activity, BMI, hormone replacement therapy status, 2005 HEI diet quality score, and total energy intake.

Table 3. Incidence of Diabetes Between 1993 and 2005 According to 100% Fruit Juice Consumption in 114,219 Postmenopausal US Women

	Quintiles of 100% Fruit Juice Consumption					P for Trend
	I	II	III	IV	V	
Range oz./d of 100% fruit juice	**0-1.0**	**1.1-2.2**	**2.3-4.0**	**4.1-6.6**	**6.7-36.8**	
Person-years of follow-up	167,457	167,857	167,421	167,277	167,721	
Number of incident cases	2329	2275	2315	2314	2255	
Incidence rate, per 1000 person-years	13.9	13.5	13.8	13.8	13.4	
Univariate hazard ratio (95% CI)	1.0 (ref)	0.97 (0.92-1.03)	0.99 (0.94-1.05)	0.99 (0.94-1.05)	0.97 (0.91-1.02)	0.74
Multivariable-adjusted* hazard ratio (95% CI)	1.0 (ref)	0.98 (0.92-1.04)	0.99 (0.94-1.05)	1.00 (0.94-1.06)	0.98 (0.92-1.04)	0.26

*Adjusted for age, education level, race/ethnicity, smoking status, physical activity, BMI, hormone replacement therapy status, 2005 HEI diet quality score, and total energy intake.

Table 4. Incidence of Hypertension Between 1993 and 2005 According to Whole Fruit Consumption in 80,539 Postmenopausal US Women						
	Quintiles of 100% Fruit Juice Consumption					**P for Trend**
	I	**II**	**III**	**IV**	**V**	
Range oz./d of 100% fruit juice	**0-1.0**	**1.0-2.1**	**2.2-4.0**	**4.1-6.6**	**6.7-36.8**	
Person-years of follow-up	92,241	91,812	91,647	91,953	91,494	
Number of incident cases	9244	9239	9263	9214	9242	
Incidence rate, per 1000 person-years	100	101	101	100	101	
Univariate hazard ratio (95% CI)	1.0 (ref)	1.01 (0.98-1.04)	1.02 (0.99-1.05)	1.00 (0.97-1.03)	1.02 (0.99-1.05)	0.71
Multivariable-adjusted* hazard ratio (95% CI)	1.0 (ref)	1.00 (0.97-1.04)	1.02 (0.98-1.05)	1.00 (0.97-1.04)	1.02 (0.98-1.05)	0.85
*Adjusted for age, education level, race/ethnicity, smoking status, physical activity, BMI, hormone replacement therapy status, 2005 HEI diet quality score, and total energy intake.						

Table 5. Incidence of Diabetes Between 1993 and 2005 According to Whole Fruit Consumption in 114,219 Postmenopausal US Women						
	Quintiles of 100% Fruit Juice Consumption					**P for Trend**
	I	**II**	**III**	**IV**	**V**	
Range oz./d of 100% fruit juice	**0-1.0**	**1.1-2.2**	**2.3-4.0**	**4.1-6.6**	**6.7-36.8**	
Person-years of follow-up	167,457	167,857	167,421	167,277	167,721	
Number of incident cases	2329	2406	2255	2217	2281	
Incidence rate, per 1000 person-years	13.9	14.4	13.4	13.2	13.6	
Univariate hazard ratio (95% CI)	1.0 (ref)	1.03 (0.98-1.10)	0.97 (0.91-1.02)	0.95 (0.90-1.01)	0.98 (0.92-1.04)	0.03
Multivariable-adjusted* hazard ratio (95% CI)	1.0 (ref)	1.05 (0.99-1.12)	0.99 (0.92-1.06)	0.98 (0.91-1.05)	1.03 (0.96-1.10)	0.05
*Adjusted for age, education level, race/ethnicity, smoking status, physical activity, BMI, hormone replacement therapy status, 2005 HEI diet quality score, and total energy intake.						

Table 6. Multivariable-Adjusted Relationships of 100% Fruit Juice and Whole Fruit with Incident Hypertension and Diabetes in Postmenopausal US Women: Sensitivity Analyses

	Multivariable Adjusted* Hazard Ratios (95% CI) comparing highest to lowest quintiles of consumption			
	Incident HTN & 100% Fruit Juice	Incident HTN & Whole Fruit	Incident Diabetes & 100% Fruit Juice	Incident Diabetes & Whole Fruit
Baseline Age < 60	0.96 (0.91-1.01)	1.03 (0.97-1.09)	0.99 (0.89-1.10)	0.97 (0.86-1.10)
Baseline Age 60-69	1.02 (0.97-1.07)	1.01 (0.96-1.07)	0.93 (0.85-1.02)	1.06 (0.95-1.18)
Baseline Age >70	1.02 (0.96-1.10)	0.99 (0.91-1.07)	1.04 (0.91-1.19)	1.05 (0.90-1.22)
OS participants only	1.00 (0.96-1.03)	1.02 (0.98-1.06)	0.98 (0.91-1.05)	1.01 (0.93-1.10)
DM CT participants only	1.02 (0.95-1.09)	0.99 (0.91-1.07)	0.95 (0.83-1.10)	1.02 (0.87-1.21)
3-year change analysis[#]	0.98 (0.94-1.01)	0.98 (0.94-1.01)	0.95 (0.88-1.02)	1.03 (0.96-1.11)

*Adjusted for age, education level, race/ethnicity, smoking status, physical activity, BMI, hormone replacement therapy status, 2005 HEI diet quality score, and total energy intake.

[#]Change analysis examined the association of change over 3 year-time periods in servings/day of the exposure (100% fruit juice or whole fruit) with the incidence of the outcome (incident hypertension or diabetes) over the same 3-year time period. The highest quintile of change was compared to the middle quintile (no change).

Table 7A. Incidence of Hypertension Between 1993 and 2005 According to 100% Fruit Juice and Whole Fruit Consumption in 80,539 Postmenopausal US Women: Sensitivity Analyses Using Cut-points

	100% Fruit Juice			Whole Fruit		
	N	IR, per 1000 PY	Multivariable Adj HR (95% CI)	N	IR, per 1000 PY	Multivariable Adj HR (95% CI)
≤ 4 serv/week	42,854	2.8	1.0 (ref)	19,651	2.7	1.0 (ref)
5-6 serv/week	16,530	2.7	0.99 (0.97-1.01)	23,933	2.8	1.01 (0.99-1.04)
1 serv/d	17,905	2.8	1.01 (0.99-1.04)	23,530	2.8	1.01 (0.98-1.05)
2-3 serv/d	2647	2.9	1.04 (0.99-1.10)	12,397	2.8	1.02 (0.98-1.05)
≥ 4 serv/d	159	3.4	1.29 (1.06-1.57)	584	2.6	0.94 (0.83-1.05)
P for Trend	0.21			0.73		

*Adjusted for age, education level, race/ethnicity, smoking status, physical activity, BMI, hormone replacement therapy status, 2005 HEI diet quality score, and total energy intake.

Adj = adjusted; IR = incidence rate; PY = person-years; serv = servings; /d = per day

Table 7B. Incidence of Diabetes Between 1993 and 2005 According to 100% Fruit Juice and Whole Fruit Consumption in 114,219 Postmenopausal US Women: Sensitivity Analyses Using Cut-points

	100% Fruit Juice			Whole Fruit		
	N	IR, per 1000 PY	Multivariable Adj HR (95% CI)	N	IR, per 1000 PY	Multivariable Adj HR (95% CI)
≤ 4 serv/week	59,226	13.8	1.0 (ref)	28,633	13.8	1.0 (ref)
5-6 serv/week	24,010	13.9	1.01 (0.97-1.07)	34,213	14.1	1.05 (0.99-1.11)
1 serv/d	26,142	13.5	0.98 (0.93-1.03)	32,771	13.4	1.00 (0.94-1.06)
2-3 serv/d	3972	13.4	0.98 (0.88-1.09)	17,180	13.5	1.04 (0.96-1.11)
≥ 4 serv/d	253	10.5	0.82 (0.53-1.27)	806	13.3	0.96 (0.75-1.21)
P for Trend	0.21			0.10		

*Adjusted for age, education level, race/ethnicity, smoking status, physical activity, BMI, hormone replacement therapy status, 2005 HEI diet quality score, and total energy intake.

Adj = adjusted; IR = incidence rate; PY = person-years; serv = servings; /d = per day

Supplemental Table A. Hierarchical Exclusions for Incident Hypertension		
Exclusions	**DM Controls (N = 29,294)**	**OS (N = 93,679)**
Reported energy intake < 600 kcal/d or > 5000 kcal/d	3,614	
Baseline 100% fruit juice not reported	174	
Baseline history of hypertension	38,646	
Total for Hypertension Analysis	80,539	

Supplemental Table B. Hierarchical Exclusions for Incident Diabetes		
Exclusions	**DM Controls (N = 29,294)**	**OS (N = 93,679)**
Reported energy intake < 600 kcal/d or > 5000 kcal/d	3,614	
Baseline 100% fruit juice not reported	174	
Baseline history of diabetes	4,966	
Total for Diabetes Analysis	114,219	

Supplemental Table C. Quintiles of Mean ± SD Whole Fruit Consumption					
	Quintile				
	I	II	III	IV	V
Hypertension analysis	0.31 ± 0.13	0.65 ± 0.09	0.94 ± 0.09	1.59 ± 0.18	2.54 ± 0.61
Diabetes analysis	0.30 ± 0.13	0.64 ± 0.09	0.93 ± 0.09	1.57 ± 0.20	2.53 ± 0.61

Abbreviations

Adj (adjusted)
BMI (body mass index)
CVD (cardiovascular disease)
/d (per day)
HEI (Healthy Eating Index)
HR (hazard ratio)
HTN (hypertension)
IR (incidence rate)
kcal (Killicalories)
MET (Metabolic Equivalent of Task)
mmHg (millimeters of mercury)
Oz. (ounce)
RCT (randomized controlled trial)
Ref (reference)
RR (relative risk)
Serv (servings)
PY (person-years)

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