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Fruits and vegetables intake and risk of frailty in women aged 60 and older

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Running head: Fruits, vegetables and frailty in women

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34

35 Abbreviations:

36 FFQ – Food frequency questionnaire

37 HR – Hazard ratio

38 NHS – Nurses’ Health Study

39

40 Abstract

41 **Background:** Prior research has suggested that the anti-oxidative and anti-inflammatory  
42 potential of fruits and vegetables may reduce pre-mature aging.

43 **Objective:** To prospectively examine the association between fruits and vegetables intake and  
44 incident frailty in older women.

45 **Design:** 78,366 non-frail women aged 60+ from the Nurses' Health Study were followed from  
46 1990 to 2014. In this analysis, the primary exposure was the intake of total fruits and vegetables,  
47 assessed with a food frequency questionnaire administered six times during follow-up. Frailty  
48 was defined as having at least three of the following five criteria from the FRAIL scale: fatigue,  
49 poor strength, low aerobic capacity, having  $\geq 5$  illnesses, and  $\geq 5\%$  weight loss. Cox models  
50 adjusted for potential confounders were used to estimate hazard ratios (HRs) and 95%  
51 confidence intervals for the association between fruits and vegetables intake and incident frailty.

52 **Results:** 12,434 (15.9%) incident frailty cases were accrued during follow-up. Total fruits and  
53 vegetable intake were associated with a lower risk of frailty (adjusted HR comparing 7+  
54 servings/d vs  $<3$ d/ = 0.89, 95% CI = 0.83, 0.96). The inverse association appeared to be stronger  
55 for those with physical activity above the median (p interaction $<0.05$ ). Among physically active  
56 women who consumed more total fruits and vegetables, when compared with those consumed  
57 less than 3 servings a day, the HR for 7+ servings/d was 0.68 (0.57, 0.81).

58 **Conclusion:** Higher fruits and vegetables intake was associated with a lower risk of frailty in  
59 this cohort of age 60+ U.S. women. Because of limited evidence on intakes of fruits and  
60 vegetables and the development of frailty, more data is needed to confirm our results.

61

62 **Keywords:** women, frailty, nutrition, fruits, vegetables, elderly

## 63 Introduction

64           Frailty in older adults involves declining physical function and increased vulnerability to  
65 illness and disability over time (1). While physical function is a major component of frailty, this  
66 syndrome also includes weight loss and other characteristics that compromise the ability to  
67 handle stressors such as acute illnesses (2). Frailty has been associated with a poor quality of life,  
68 as well as increased morbidity and mortality (3-6).

69           Dietary patterns that are characterized by high intakes of fruits and vegetables have  
70 shown to be associated with a lower risk of frailty (7-9). Fruits and vegetables may influence the  
71 rate of functional decline in the elderly through reducing excessive oxidative stress and  
72 inflammation by reducing pre-mature aging (10-12). In addition, fruits and vegetables also  
73 contain components (e.g. fiber, potassium) that may reduce the risk of major chronic diseases  
74 (13).

75           A few small prospective studies have observed an inverse association between fruits and  
76 vegetables intake and frailty (14). However, because their follow-up duration was less than 5  
77 years, these studies could only examine short term associations (8, 15). In addition, the results  
78 were mixed, with an inverse association for both fruits and vegetables for a combined French and  
79 Spanish study (15), an inverse association with fruits but not vegetables in a Spanish study (8),  
80 and an inverse association only with vegetables that were not salads, carrots, or potatoes in an  
81 African-American cohort (16). On the other hand, a previous study from the Nurses' Health  
82 Study on diet quality and physical function noted an inverse association with higher intakes of  
83 fruits and vegetables (17). Other commonly considered features of geriatric frailty, such as  
84 fatigue, unintentional weight loss, and chronic illness (1, 18), may also contribute independently  
85 or compound poor physical function. Among participants in the Nurses' Health Study (NHS)

who had diabetes, higher fruits and vegetables intake was associated with a lower risk of frailty (19). However, the association was attenuated upon additional adjustment for physical activity. Therefore, we expanded our analysis to the entire NHS cohort and prospectively examined intake of total fruits and vegetables in relation to development of frailty, which includes multiple assessments of diet and a long follow-up.

## Methods

### Study participants

Women in this analysis were participants of the U.S. Nurses' Health Study. This ongoing cohort began in 1976 with 121,700 nurses aged 30–55 y in 11 states (20). Participants self-reported lifestyle and disease information through a questionnaire every 2 years. In addition, a food-frequency questionnaire (FFQ) was sent in 1980, 1984, 1986, and every 4 years thereafter to collect dietary information.

In this analysis we included women aged  $\geq 60$  years in 1992 with valid (intake between 500 and 3500kcal/d) dietary information from the 1990 FFQ, or from the 1986 FFQ if the 1990 FFQ was not available. We used 1992 as baseline for this analysis as it was the first time frailty characteristics were assessed. Women younger than age 60 at 1992 entered follow-up when they reached age 60 in subsequent questionnaire cycles if they also have returned an FFQ in 1990. After excluding those who met the frailty criteria for this study at entry to follow-up, data from 78,366 women were included for analysis and followed up to 2014 (**Supplemental figure 1**). The Harvard School of Public Health and Brigham and Women's Hospital Institutional Review Board approved the protocol of the study.

## Dietary assessment

Dietary intake was assessed at baseline and in 1994, 1998, 2002, 2006, and 2010 using a validated self-administered semi-quantitative FFQ (21) that contained approximately 135 items. It included approximately 25 vegetables, 9 whole fruits, and 3 juice items. Standard portion size was provided for each item and nine frequency choices, ranging from <1 time/month to  $\geq 6$  times/day were available. In this analysis, we considered all vegetables and only whole fruits. In validation studies, the deattenuated correlation coefficients ranged from 0.16 (yellow squash) to 0.53 (string beans) among vegetables, and 0.50 (oranges) to 0.74 (apples) among fruits (22) as measured by the FFQ and multiple-weeks food records. In addition, biomarkers sensitive to fruits and vegetables intake such as specific carotenoids and folate were strongly associated with intakes of these nutrients based on our FFQ (23).

## Assessment of frailty

Frailty is defined using the FRAIL scale that comprises five self-reported criteria: fatigue, reduced capacity for resistance physical activity, low aerobic capacity, history several major chronic illnesses, and a significant weight loss during the previous year (18). The FRAIL scale correlates well with the Fried frailty phenotype, and it has been adapted and validated to be used in several populations (24-26). In 1992, 1996, 2000, 2004, 2008 and 2012 participants completed the Medical Outcomes Study Short-Form (SF-36), a 36-item-questionnaire with eight health dimensions, including physical and mental components (27). From the SF-36, we assessed the first three frailty criteria with the following questions: a) for fatigue: "Did you have a lot of energy?", with replies "some of the time" or "none of the time" or with the question "I could not get going", with responses "moderate amount" or "all of the time"; b) for poor strength (low

resistance): “In a normal day, is your health a limitation to walk up 1 flight of stairs?”, with responses “yes” or “a lot”; and c) for low aerobic capacity: “In a normal day, is your health a limitation to walk several blocks or several miles?”, with responses “yes” or “a lot”. In addition, the illnesses criterion was ascertained from the question “In the last 2 years, have you had any of these physician-diagnosed illnesses?” Participants reporting  $\geq 5$  of the following diseases were considered to meet this criterion: cancer, hypertension, type 2 diabetes, angina, myocardial infarction, stroke, congestive heart failure, asthma, arthritis, chronic obstructive lung disease, Parkinson’s disease, kidney disease, and depression. Finally, the weight loss criterion was defined as a  $\geq 5\%$  decrease in the weight reported in two consecutive follow-up cycles. At the end of each follow-up cycle, incident cases of frailty were defined as participants having  $\geq 3$  criteria in the FRAIL scale. Missing response in 3 or more components was assumed as missing on frailty status and excluded. For those with one or two missing responses, we were able to assess frailty status, considering missing in each characteristic as not having it.

#### Assessment of health and lifestyle characteristics

Participants self-reported height in 1976 was used to calculate updated Body Mass Index (BMI) with weight reported at each biennial questionnaire. Also assessed every two years were smoking status and the quantity of cigarette use, use of brand-specific multivitamins (yes or no), physical activity, use of medication for hypertension, diabetes, and hyperlipidemia, and postmenopausal hormone. Recreational physical activity was assessed with 10 activities and reported as hours per week and were assigned a metabolic equivalent score. These scores were then summed over all activities to create a value in metabolic equivalent task hours per week (28).



155

## 156 Statistical analysis

157       The primary exposure in this analysis was total fruits and vegetables intake. We  
158 computed cumulative averages from each FFQ to reduce within-person variation and represent  
159 long-term intake (29). For example, the average intake in 1990 and 1994 was used to predict  
160 frailty incidence between 1994 and 1996, and the average intake from 1990, 1994, and 1998  
161 were used to predict frailty incidence between 1998 and 2000. Cumulative averages were  
162 computed using available valid FFQs. The cumulative average of fruits and vegetables intake  
163 were then classified into pre-defined categories with the lowest one as the reference group and  
164 the association with incident frailty was examined using Cox proportional hazard models. Tests  
165 of trends were conducted by modeling intake as a continuous variable. We tested for  
166 proportional hazard assumption with likelihood ratio test comparing the main model and a model  
167 with interaction terms between age and the exposure and 4-year time periods and the exposure.  
168 No violation of the assumption was observed. We also explored potential differences in  
169 associations by BMI and physical activity status with stratified analysis of BMI at 25.0 and  
170 physical activity at the median. Test for interaction was performed using the likelihood ratio test  
171 comparing regression models with and without interaction terms.

172       In multivariable analysis, we adjusted for age (in months), energy intake (quintiles),  
173 alcohol intake (0, 1 to <5g/d, 5 to <10g/d, 10 to <15g/d, 15+g/d), BMI (<23, 23 to <25, 25 to  
174 <28, 28 to <30, 30+), physical activity (quintiles), smoking (never, past, current 1-14  
175 cigarettes/d, 15-24 cigarettes/d, 25+ cigarettes/d), use of aspirin, diuretics, beta blockers, calcium  
176 channel blockers, angiotensin converting enzyme inhibitors, and other antihypertensive  
177 medication, statins and other cholesterol lowering drugs, insulin, and oral hypoglycemic

medication. As part of the multivariable model, we also adjusted for indicators of socioeconomic status, as approached by the highest academic degree (high school or lower, college, graduate degree) and census tract income data (continuous). Missing data was categorized into a missing indicator. In addition, to account for other dietary characteristics, we adjusted for diet quality using a modified version of the Alternate Healthy Eating Index-2010 that omitted the fruits and vegetables components (30). Covariates were chosen based on their potential as confounders and predictors of components of the FRAIL score. We also explored the association of subgroups of fruits and vegetables intake with risk of developing frailty. In these analyses specific groups of fruits and vegetables were mutually adjusted for each other.

Although in the main analysis we included only women who did not meet the frailty criteria (i.e. having at least 3 frailty components) at baseline, some had one or two frailty components preexisting. Therefore, we repeated the analysis among those without any frailty component at baseline to explore if the association of fruits and vegetables intake on frailty may differ depending on the baseline status. We also used this subset of participants to explore the association between fruits and vegetables intake and risk of developing each criterion of the FRAIL scale. We examined non-linearity in the association by fitting restricted cubic splines. Test for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms. In addition, we examined potential reverse causation by lag time analysis, discarding the first 8 years of follow-up. Analyses were performed with the SAS software, version 9.4 (SAS Institute Inc, Cary, NC).

## Results

In up to 20 years of follow-up, 12,434 women developed frailty (15.9%). Women with higher fruits and vegetables intake tended to be more physically active, were less likely to be a current smoker, and consumed more whole grains and calcium, but less alcohol and saturated fat (Table 1). Total fruits and vegetables intake was inversely associated with the risk of developing frailty (Table 2). In age and energy adjusted model, the hazard ratio (HR) for women who consumed 7 or more servings of fruits and vegetables per day was 0.55 (95% CI=0.51, 0.59,  $p$  for trend=0.03) compared with those with less than 3 servings. The multivariable HR for the same comparison of fruits and vegetables per day was 0.92 (95% CI=0.85, 0.99). We also observed a significant inverse trend ( $p=0.01$ ) for fruit intake. The test for non-linearity was not significant. While the inverse association with total fruits and vegetables did not differ by BMI status (Table 3), it appeared to be stronger for those with physical activity above the median ( $p$  interaction <0.05). Among physically active women who consumed more total fruits and vegetables, when compared with those consumed less than 3 servings a day, the HR was 0.75 (95% CI = 0.63, 0.88) for 4 to <5 servings/d, 0.76 (0.64, 0.91) for 5 to <6 servings/d, 0.70 (0.59, 0.84) for 6 to <7 servings/d, and 0.68 (0.57, 0.81) for 7+ servings/d.

Among women without any frailty component at entry to follow-up, 6288 frailty incident occurred during follow-up. An inverse association was observed when comparing 4+ servings/day with <1/day of fruits intake (RR=0.83, 95% CI = 0.72, 0.96) (Supplemental table 1). When we examined each frailty component, the most consistent finding appeared to be for fatigue, with independent inverse association for intake of total fruits and vegetables (HR comparing 7+ to <3 servings/day = 0.81, 95% CI = 0.76, 0.86), vegetables (HR for 5+ servings = 0.83, 95% CI = 0.78, 0.88), and fruits (HR for 4+ servings = 0.82, 95% CI= 0.76, 0.89) (Supplemental table 2). When we explored the association of specific types of fruits and

**Comentado [ELG1]:** I couldn't review supplemental tables since they weren't in the email!

vegetables, we observed a clear inverse association with leafy vegetables (p for trend <0.001), yellow vegetables (p for trend <0.001), and apples and pears (p for trend <0.001) (Supplemental table 4).

Results for 8-year lag analysis (10,068 cases) showed some attenuation of the association but the linear trend remained statistically significant for total fruits (p = 0.006) (supplemental table 5).

## Discussion

We observed a clear inverse trend between total fruits and vegetables intake and the risk of developing frailty among women age 60 or older. The association was similar regardless of BMI status. While this association was observed in women both above and below the physical activity median, it was particularly strong for those above the physical activity median.

Existing data on fruits and vegetables intake and frailty is sparse and composed of relatively small studies. Results were a mix of no association (8, 31), and inverse association separately for fruits, vegetables (15), or specific vegetable group (16). Most of these studies also lacked adjustment for energy intake or did not control for dietary characteristics (8, 16, 31). In some studies, the measurement of diet was crude and consisted of questions on overall fruits or vegetables intake without information on specific fruits and vegetables (16, 31). In contrast, our FFQ has approximately 37 fruits and vegetables items. This comprehensive assessment of intake allowed us to examine the association of specific fruits and vegetable groups with frailty outcomes.

Antioxidants in fruits and vegetables may limit excessive oxidative stress which plays a role in inflammation, and in turn may accelerate aging and frailty development (33-35).

Excessive oxidation may impair muscle preservation in aging, resulting in sarcopenia that leads to poor strength and reduced physical function (36). Serum carotenoids level was shown to be inversely associated with muscle strength decline (37). Thus, this could also be a pathway through which fruits and vegetables intake may contribute to the development of frailty. In addition, fiber and other phytochemicals may reduce the risk of cardiovascular and other chronic diseases (13), of which poor physical function could be a sequelae. Phytochemicals and antioxidant nutrients such as vitamin C may also improve immune function in the older adults through cell-mediated and non-cell mediated pathways (10), thus preserving ambulation ability and physical functioning. Some fruits have high glycemic index and different fruits and vegetables vary greatly in polyphenols, vitamins and sugar content, which may contribute to the different results observed in individual fruits and vegetable groups.

Obesity has been associated with functional decline (38) and the development of frailty (39-41). Increased oxidative stress due to higher levels of circulating inflammatory molecules may reduce the already lower anabolic activities in muscles in aging (42). This may exacerbate functional decline and accelerate progression to disability. In our analysis, obesity was not a clear effect modifier and the association between total fruits and vegetables intake appeared to be independent of obesity. On the other hand, we noted potential interaction with physical activity with stronger association among women with higher fruits and vegetables intake and also physically active. Physical activity has been shown to improve physical functioning and frailty in the older people (43, 44). It may mitigate the reduced anabolic capacity in muscles through increasing activity in the IGF-1 pathway (45). When this is coupled with antioxidants in fruits and vegetables to reduce the catabolic effect of oxidative stress on muscle in aging, physical activity and a healthy diet thus may potentially be a powerful combination to preserve muscle

mass and physical functioning. In addition, both physical activity (46) and fruits and vegetables intake (47) are associated with lower risk of chronic diseases, a key determinant of disability (48). Therefore, the combination of high physical activity and a healthy diet characterized by high fruits and vegetables intake may have additive or synergistic potential in preventing frailty.

The strengths of this study included detailed and repeated dietary information which allowed us to examine different groups of fruits of vegetables as well as consider changes in consumption of these groups. We also had detailed lifestyle information for fine control of confounders. Our thorough analysis included examining the individual components of frailty and potential differential association due to pre-existing frailty characteristics.

There is no standard definition of frailty, but fatigue/exhaustion, weakness, weight loss, and sometimes presence of co-morbidities are common components (1, 18). In the absence of a uniform diagnostic criteria, previous studies used different characteristics to define frailty and also set the criteria differently based on the types of data available. For example, Garcia-Equinas (15) assessed the exhaustion component of the Fried (1) definition of frailty with questions from the Center for Epidemiologic Studies Depression Scale, and the weakness component based on measured grip strength. On the other hand, Johannessen defined frailty with 8 characteristics such as self-reported weight loss and measured walking speed (31). In this study, we used the FRAIL scale, a definition of frailty based on an international consensus for physical frailty (32) and used self-reported data to determine fulfillment. The varied definition complicates the comparison of results in the existing literature but nevertheless, our results do support fruits and vegetables intake having an association with the development of frailty. In the present analysis, we adapted the exact questions in the FRAIL scale (18) in the NHS questionnaires. The FRAIL scale included questions based on self-reported information. However, it has been shown to be

correlated ( $r=0.617$ ,  $p<0.001$ ) with the Fried scale (1), the most widely used scale for frailty assessment, which includes both self-reported and performance-based measures.

Frailty can detrimentally affect the ability to prepare food and may therefore limit fruits and vegetables intake in affected individuals. This may explain the weak direct association observed in some fruits and vegetable groups as our extensive food list contains items such as prunes and canned fruits that may be more highly used by individuals who have some physical impairment. This also contributes to the complexity in the study of body weight and mortality. Although the potential for reverse causation in this analysis was reduced due to its prospective nature, reversed causation cannot be totally discounted. While results for the lag-8-years analysis were weaker, a signal for an inverse association for fruits and vegetables was nevertheless observed. As in all observational studies, complete elimination of confounding is difficult. However, we adjusted for a broad range of lifestyle, socioeconomic variables, and dietary factors in finely categorized groups. In addition, with repeated measurements of lifestyle and diet, we were able to update these potential confounders throughout follow-up. Therefore, any residual confounding should be small. Finally, since several definitions of frailty exist, our results should be confirmed in studies using other definitions such as the Fried scale or the Rockwood index (49).

In conclusion, in this U.S. cohort of nurses age 60 and older, fruits and vegetables intake was associated with lower risk of frailty. The inverse association was particularly strong when high fruits and vegetables intake was combined with high levels of physical activity. While additional data is needed to confirm our results, this study adds to the evidence that supports the role of fruits and vegetables intake in decreasing the risk of individual chronic diseases.

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317 research, TF conducted the analysis and have primary responsibility for final content, all authors  
318 provided input on design, analytical procedure, and content, all authors have read and approved  
319 the manuscript.

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Table 1: Lifestyle and dietary characteristics (mean  $\pm$  SD) by categories of total fruits and vegetables intake (servings/day) at age 60 <sup>1</sup> (n=78,366)

	< 3	3 to < 4	4 to < 5	5 to < 6	6 to < 7	7+
BMI (kg/m <sup>2</sup> )	25.5 $\pm$ 5.2	25.5 $\pm$ 5.2	25.5 $\pm$ 5.1	25.4 $\pm$ 5.1	25.2 $\pm$ 5.1	25.2 $\pm$ 5.0
Physical activity (MET hr/wk) <sup>2</sup>	7.7 $\pm$ 13.7	8.8 $\pm$ 15.1	10.0 $\pm$ 14.8	11.3 $\pm$ 16.5	12.7 $\pm$ 18.7	16.1 $\pm$ 24.5
Current smoker (%)	7.6	5.4	4.4	3.8	3.3	2.8
<b>Medication use (% yes)</b>						
Post menopausal hormone	6.5	7.8	8.2	8.0	8.6	8.9
Diuretics	12.6	15.2	15.3	15.1	15.0	14.5
Beta blockers	16.9	19.5	19.1	19.0	19.2	17.4
Calcium channel blockers	12.5	14.0	14.1	13.8	13.5	13.4
Other antihypertensive medication	7.5	7.9	7.5	7.5	6.9	6.9
ACE inhibitors	7.4	9.0	8.8	9.1	9.0	8.4
Statins	34.6	38.5	37.6	37.1	35.5	32.9
Other lipid lowering medication	4.7	5.0	5.1	4.7	5.2	5.1
Insulin	2.2	2.5	2.2	2.3	2.1	1.9
Oral hypoglycemics	3.4	3.7	3.4	3.0	3.4	2.8
<b>Dietary intake</b>						
Energy (kcal/d)	1250 $\pm$ 433	1429 $\pm$ 443	1569 $\pm$ 466	1691 $\pm$ 473	1804 $\pm$ 494	2062 $\pm$ 535
Protein <sup>3</sup> (g/d)	64.1 $\pm$ 14.0	66.0 $\pm$ 13.0	70.0 $\pm$ 12.6	67.7 $\pm$ 12.5	68.3 $\pm$ 12.3	69.0 $\pm$ 12.5
Alcohol (g/d)	4.8 $\pm$ 10.3	5.3 $\pm$ 10.2	5.5 $\pm$ 10.1	5.6 $\pm$ 10.0	5.7 $\pm$ 9.8	5.6 $\pm$ 9.8
Saturated fat <sup>3</sup> (g/d)	20.6 $\pm$ 5.7	18.8 $\pm$ 4.9	17.9 $\pm$ 4.6	17.3 $\pm$ 4.5	16.7 $\pm$ 4.3	15.3 $\pm$ 4.1
Whole grains <sup>3</sup> (g/day)	33.2 $\pm$ 22.4	34.7 $\pm$ 20.4	35.3 $\pm$ 19.1	35.3 $\pm$ 18.3	35.6 $\pm$ 17.8	35.8 $\pm$ 17.1
Total vegetables & fruit (servings/day)	2.1 $\pm$ 0.7	3.5 $\pm$ 0.3	4.5 $\pm$ 0.3	5.5 $\pm$ 0.3	6.5 $\pm$ 0.3	9.1 $\pm$ 2.1
Total vegetables (servings/day)	1.2 $\pm$ 0.6	1.9 $\pm$ 0.6	2.4 $\pm$ 0.7	3.0 $\pm$ 0.8	3.6 $\pm$ 1.0	5.1 $\pm$ 1.8
Total fruit (servings/day)	0.9 $\pm$ 0.6	1.6 $\pm$ 0.6	2.1 $\pm$ 0.7	2.5 $\pm$ 0.8	2.9 $\pm$ 0.9	3.9 $\pm$ 1.5
Cruciferous vegetables (servings/day)	0.2 $\pm$ 0.1	0.2 $\pm$ 0.2	0.3 $\pm$ 0.2	0.4 $\pm$ 0.3	0.5 $\pm$ 0.3	0.7 $\pm$ 0.5
Yellow/orange vegetables (servings/day)	0.2 $\pm$ 0.2	0.3 $\pm$ 0.2	0.3 $\pm$ 0.3	0.5 $\pm$ 0.3	0.6 $\pm$ 0.4	0.8 $\pm$ 0.6
Tomatoes (servings/day)	0.3 $\pm$ 0.3	0.5 $\pm$ 0.3	0.6 $\pm$ 0.4	0.7 $\pm$ 0.4	0.8 $\pm$ 0.4	1.0 $\pm$ 0.6
Leafy vegetables (servings/day)	0.2 $\pm$ 0.2	0.4 $\pm$ 0.3	0.6 $\pm$ 0.4	0.7 $\pm$ 0.4	0.8 $\pm$ 0.4	1.1 $\pm$ 0.7
Other vegetables (servings/day)	0.3 $\pm$ 0.2	0.5 $\pm$ 0.3	0.7 $\pm$ 0.4	0.8 $\pm$ 0.5	1.0 $\pm$ 0.5	1.5 $\pm$ 0.8
Citrus fruits (servings/day)	0.07 $\pm$ 0.1	0.1 $\pm$ 0.2	0.2 $\pm$ 0.3	0.2 $\pm$ 0.3	0.3 $\pm$ 0.3	0.4 $\pm$ 0.5
Apples& pears (servings/day)	0.09 $\pm$ 0.1	0.2 $\pm$ 0.2	0.2 $\pm$ 0.2	0.3 $\pm$ 0.3	0.3 $\pm$ 0.3	0.5 $\pm$ 0.4
Berries (servings/day)	0.1 $\pm$ 0.1	0.2 $\pm$ 0.2	0.2 $\pm$ 0.3	0.3 $\pm$ 0.3	0.4 $\pm$ 0.4	0.5 $\pm$ 0.5

<sup>1</sup> All p value for trend <0.05 except for other lipid lowering medication, p value computed by generalized linear models.

<sup>2</sup>Metabolic Equivalent hours/week<sup>3</sup>energy adjusted

Table 2: Hazard ratios (95% CI) for frailty by categories of fruits and vegetables intake (servings/day) (n=78,366)

<b>Total fruits and vegetables</b>	<b>&lt; 3</b>	<b>3 to &lt; 4</b>	<b>4 to &lt; 5</b>	<b>5 to &lt; 6</b>	<b>6 to &lt; 7</b>	<b>7+</b>	<b>P for trend</b>
Number of cases	1620	2199	2362	2248	1628	2377	
Person years	118,894	165,204	208,165	202,222	157,829	273,616	
Age and energy adjusted	1	0.87 (0.82, 0.93)	0.72 (0.68, 0.77)	0.69 (0.65, 0.74)	0.64 (0.59, 0.69)	0.55 (0.51, 0.59)	<0.001
Multivariable adjusted <sup>1</sup>	1	1.01 (0.95, 1.08)	0.91 (0.85, 0.97)	0.96 (0.89, 1.03)	0.94 (0.87, 1.01)	0.92 (0.85, 0.99)	0.03

  

<b>Total vegetables</b>	<b>&lt; 2</b>	<b>2 to &lt; 3</b>	<b>3 to &lt; 4</b>	<b>4 to &lt; 5</b>	<b>5+</b>		
Number of cases	3275	3834	2810	1410	1105		
Person years	246,374	329,971	266,152	151,245	132,188		
Age and energy adjusted	1	0.84 (0.80, 0.88)	0.77 (0.73, 0.81)	0.69 (0.65, 0.74)	0.67 (0.62, 0.72)		<0.001
Multivariable adjusted <sup>1</sup>	1	0.98 (0.94, 1.03)	0.97 (0.92, 1.03)	0.94 (0.88, 1.01)	0.99 (0.92, 1.07)		0.24

  

<b>Total fruits</b>	<b>&lt; 1</b>	<b>1 to &lt; 2</b>	<b>2 to &lt; 3</b>	<b>3 to &lt; 4</b>	<b>4 +</b>		
Number of cases	1257	4173	4150	1939	915		
Person years	105,712	340,925	371,258	195,286	112,749		
Age and energy adjusted	1	0.86 (0.81, 0.92)	0.73 (0.68, 0.78)	0.64 (0.59, 0.68)	0.56 (0.51, 0.62)		<0.001
Multivariable adjusted <sup>1</sup>	1	0.97 (0.90, 1.03)	0.94 (0.88, 1.01)	0.92 (0.85, 1.00)	0.91 (0.83, 1.00)		0.01

<sup>1</sup>Adjusted for age, smoking, energy intake, BMI, physical activity, post menopausal hormone use, aspirin, antihypertensive medications, lipid lowering medications, diabetes medication, insulin, highest academic degree, census tract income data, alcohol, and a modified Alternate Healthy Eating Index that does not include fruits and vegetables. Hazard ratios computed with Cox proportional hazard models.

Table 3: Multivariable<sup>1</sup> hazard ratios (95% CI) of fruits and vegetables intake and risk of frailty, stratified by BMI<sup>2</sup> and physical activity<sup>3</sup>. (n=78,366)

<b>Total fruits and vegetables</b>	<b>&lt; 3</b>	<b>3 to &lt; 4</b>	<b>4 to &lt; 5</b>	<b>5 to &lt; 6</b>	<b>6 to &lt; 7</b>	<b>7+</b>	<b>P for trend</b>
BMI < 25.0	1	0.98 (0.88, 1.08)	0.88 (0.79, 0.97)	0.94 (0.84, 1.04)	0.97 (0.86, 1.09)	0.89 (0.79, 1.01)	0.11
BMI ≥ 25.0	1	1.05 (0.96, 1.15)	0.95 (0.87, 1.04)	0.98 (0.89, 1.08)	0.93 (0.84, 1.03)	0.96 (0.86, 1.06)	0.21
Physical activity < median	1	0.98 (0.91, 1.06)	0.87 (0.80, 0.94)	0.90 (0.83, 0.97)	0.89 (0.81, 0.97)	0.86 (0.79, 0.94)	<0.001
Physical activity ≥ median	1	0.88 (0.74, 1.05)	0.75 (0.63, 0.88)	0.76 (0.64, 0.91)	0.70 (0.59, 0.84)	0.68 (0.57, 0.81)	<0.001
<b>Total vegetables</b>	<b>&lt; 2</b>	<b>2 to &lt; 3</b>	<b>3 to &lt; 4</b>	<b>4 to &lt; 5</b>	<b>5+</b>		
BMI < 25.0	1	0.98 (0.91, 1.05)	0.91 (0.89, 1.06)	0.93 (0.84, 1.04)	0.99 (0.87, 1.12)		0.17
BMI ≥ 25.0	1	1.01 (0.94, 1.08)	0.99 (0.92, 1.07)	0.97 (0.89, 1.07)	1.03 (0.93, 1.14)		0.92
Physical activity < median	1	0.96 (0.91, 1.01)	0.94 (0.88, 0.99)	0.90 (0.83, 0.97)	0.85 (0.86, 1.04)		0.02
Physical activity ≥ median	1	0.88 (0.79, 0.99)	0.84 (0.74, 0.96)	0.81 (0.69, 0.93)	0.84 (0.72, 0.99)		0.01
<b>Total fruits</b>	<b>&lt; 1</b>	<b>1 to &lt; 2</b>	<b>2 to &lt; 3</b>	<b>3 to &lt; 4</b>	<b>4 +</b>		
BMI < 25.0	1	0.97 (0.87, 1.08)	0.94 (0.85, 1.05)	0.94 (0.83, 1.06)	0.93 (0.81, 1.08)		0.23
BMI ≥ 25.0	1	0.96 (0.88, 1.05)	0.94 (0.86, 1.03)	0.91 (0.82, 1.01)	0.89 (0.78, 1.01)		0.01
Physical activity < median	1	0.94 (0.87, 1.01)	0.88 (0.81, 0.95)	0.89 (0.81, 0.97)	0.87 (0.77, 0.97)		0.001
Physical activity ≥ median	1	0.86 (0.73, 1.02)	0.83 (0.70, 0.98)	0.69 (0.58, 0.83)	0.72 (0.58, 0.89)		<0.001

<sup>1</sup>Adjusted for age, smoking, energy intake, BMI, physical activity, post menopausal hormone use, aspirin, antihypertensive medications, lipid lowering medications, diabetes medication, insulin, highest academic degree, census tract income data, alcohol, and a modified Alternate Healthy Eating Index that does not include fruits and vegetables. Hazard ratios computed with Cox proportional hazard models.

<sup>2</sup> Case count: BMI <25 = 5336, BMI ≥25 = 7098; p interaction= <0.05 for total fruits and vegetables and total vegetables

<sup>3</sup> Case count: Physical activity < median = 9559, Physical activity ≥ median = 2875; p interaction= <0.05 for total vegetables, total fruit, and total fruits and vegetables