Published in final edited form as:
Med Sci Sports Exerc. 2014 February ; 46(2): 312–317. doi:10.1249/MSS.0b013e3182a4e89c.

Reduced Risk of Incident Kidney Cancer from Walking and Running

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Abstract

Purpose—Test whether incident kidney cancer risk is associated with exercise energy expenditure (i.e., metabolic equivalents, 1 MET) when calculated from distance walked or run.

Methods—Hazard ratios (HR) and 95% confidence intervals (95%CI) from Cox proportional hazard analyses of self-reported physician-diagnosed incident kidney cancer vs. MET-hours/wk in 91,820 subjects recruited between 1991 and 1993 (7.7 yr follow-up of 42,833 subjects) and between 1998 and 1999 (6.4 yr follow-up of 33,053 subjects) as part of the National Runners' Health Study and between 1998 and 1999 as part of the National Walkers' Health Study (5.7 yr follow-up of 15,934 subjects).

Results—Fifty-two incident cancers were reported. Age- and sex-adjusted risk declined 1.9% per MET-hour/wk run or walked (HR: 0.981; 95%CI: 0.964 to 0.997, P=0.02). Compared to walking or running below guidelines levels (<7.5 MET-hours/wk), the risk for incident kidney cancer was 61% lower for meeting the guidelines (HR: 0.39, 95%CI: 0.11 to 1.08, P=0.07 for 7.5 to 12.5 MET-hours/wk), 67% lower for exercising one to two-times the recommended level (HR: 0.33; 95%CI: 0.15 to 0.72, P=0.005 for 12.6 to 25.1 MET-hours/wk), and 76.3% lower for exercising ≥2-times the recommended level (HR: 0.24; 95%CI: 0.11 to 0.52, P=0.0005 for ≥25.2 MET-hours/wk). Incident kidney cancer risk also increased in association with baseline BMI (P=0.002), smoking (P=0.02), and hypertensive (P=0.007) and diabetes medication use (P=0.01), however, exercise-associated reductions in kidney cancer risk persisted for 12.6 to 25.1 MET-hours/wk (HR: 0.35, P=0.01), and ≥ 25.2 MET-hours/wk (HR: 0.29, P=0.004) vis-à-vis <7.5 MET-hours/wk when also adjusted for BMI, hypertension, diabetes, and pack-years smoked.

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The authors declares that no competing interests exist. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

Conclusion—Running and walking may reduce incident kidney cancer risk independent of its other known risk factors.

Keywords

Prevention; prospective cohort study; renal cancer; epidemiology

Introduction

The incidence of kidney cancer in the United States has increased by 3.1% per year between 2005 to 2009 [1]. An estimated 65,150 new diagnoses and 13,680 deaths due to cancers of the kidney are expected in the US for 2013 [1]. This includes both renal cell carcinomas, representing approximately 92% of kidney cancers [16], and urothelial cell carcinomas of the renal pelvis, representing approximately 6% [1].

In addition to chemical toxins, smoking, adiposity, and hypertension are known renal cell cancer risk factors [7,16], with smoking, adiposity, and hypertension together accounting for about 49% of the risk [2]. Renal cell cancer risk may also increase with diabetes [7] and decrease with alcohol intake [7]. Greater physical activity is associated with weight loss [38] and preventing age-related weight gain [32], lower blood pressure [31] and hypertension [33], and lower fasting glucose [31] and type 2 diabetes [33], which collectively would be expected to reduce the risk of kidney cancer. Runners and walkers also tend to smoke less and drink more in relation to their exercise dose (Table 1). In addition, exercise might reduce renal cancer directly via exercise-induced decreases in estrogen, insulin, and insulin-like growth factor-I [7], factors that have been shown to promote renal carcinogenesis [11,15]. Exercise may also reduce renal cell cancer by decreasing renal cell DNA mutations from lipid peroxidation [9].

In fact, the association between kidney cancer and physical activity is currently considered unclear [7,16,40]. There have been nine cohort studies [4,5,18,23–25,28,30,39] and ten case control studies [6,12,14,17,20,21–26,27,29] that have tested their association, of which five of the cohort [4,23,24,28,39] and four of the case-control studies [6,17,22,29] have reported significant reductions in kidney cancer with physical activity. In part, the lack of evidence for leisure-time physical activity may be due to limitations in the cohort designs and survey instruments. None of the prior studies of kidney cancer and physical activity were specifically recruited for the study of physical activity, all estimated exercise energy expenditure from exercise duration, and all combined different types of exercise in estimating exercise energy expenditure. Nevertheless, approximately one-half of the reports show significantly lower kidney cancer risk with greater physical activity.

This paper tests whether the risk of incident kidney cancer is reduced in relation to exercise energy expenditure by walking or running in 91,820 men and women during a 6.9-year follow-up. The subjects were participants of the National Runners' and Walkers' Health Studies [31–38], which are the only prospective epidemiological cohorts designed specifically for testing the health benefits of physical activity. There are several potential advantages to the analyses of running and walking over the combined energy expenditure of all types of exercise. Running and walking occurs in discrete bouts, and particularly for

running, must be done with high regularity. In addition, exercise energy expenditures were calculated from weekly distance run or walked, which appears to be a much better metric for studying dose-response than the traditional time-based calculations used by other studies [34–36]. Specifically, associations with body weight, diabetes, hypertension, and high cholesterol with distance-based estimates of energy expenditure are approximately twice as great as those observed with time-based estimates [34–36]. This is important because non-differential errors in recall of physical activity are likely to bias results toward the null in most existing studies [19]. In particular, measurement error associated with other physical activity questionnaires may substantially underestimate the impact of physical activity on cancer risk [8].

Methods

The analyses are based on the combined sample from National Runners' Health Study I [31–33,38], National Runners' Health Study II [34,35], and the National Walkers' Health Study [34,36]. Each of the three cohorts are more accurately characterized as a single cohort that targeted both runners and walkers, since all three were recruited using the same questionnaire (modified slightly for the different activities), using the same sampling domain (subscription lists to running and walking publications, running and walking events), and using the same survey staff. The studies have been described in detail [31–38]. The original purpose of the cohorts was to test whether running and walking affected disease risk, however, the complete re-survey of the walkers and the National Runners' Health Study II have yet to be funded. Briefly, the 54,956 participants of the National Runners' Health Study I were recruited between 1991 and 1994 (primarily 1993), of whom 80% provided follow-up surveys 7 years after baseline or were known dead. The 63,308 runners of the National Runners' Health Study II and the 42,140 walkers of the National Walkers' Health Study were recruited in 1998 and 1999, respectively. These cohorts were partially resurveyed in 2006 to establish a population of approximately 50,000 runners and walkers for a proposed clinical trial, rather than a prospective follow-up study per se. All participants of the National Runners' Health Study II and the National Walkers' Health Study were sent surveys but recruitment ceased once 50,000 follow-up questionnaires were received. Respondents represented approximately a third of the original walkers (33.2%), and one-half of the original runners surveyed (51.7%). The difference in recruitment rates was due to the greater effort made to recruit runners (two mailings) than walkers (one mailing). Compared to non-responders, walkers and the National Runners' Health Study II participants that responded were slightly more likely to be female, younger, slightly less educated, weighed slightly more, were less likely to report taking medications for blood pressure, hypertension, or diabetes at baseline, but reported approximately the same number of km/day run if a runner or walked if a walker at baseline [34]. The 108 subjects who reported a prior history of kidney cancer on their baseline questionnaires were excluded. The study protocol was approved by the University of California Berkeley Committee for the Protection of Human Subjects, and all participants signed committee-approved informed consents.

Participants completed baseline and follow-up questionnaires on height, weight, diet, cigarette use, and medications for blood pressure and diabetes. Intakes of meat and fruit were based on the questions “During an average week, how many servings of beef, lamb, or

pork do you eat", and "…pieces of fruit do you eat". Alcohol intake was estimated from the corresponding questions for 4-oz (112 mL) glasses of wine, 12-oz (336 mL) bottles of beer, and mixed drinks and liqueurs. Alcohol was computed as 10.8 g/4-oz glass of wine, 13.2 g/12-oz bottle of beer, and 15.1 g/mixed drink. Correlations between these responses and values obtained from 4-day diet records in 110 men were r=0.65 for alcohol intake, r=0.46 for red meat, and r=0.38 for fruit. Education was solicited by requesting the participant provide "years of education (examples: HS=12; BS or BA = 16; MS or MA = 18; PhD or MD = 20)." Height and weight were determined by asking the participant, "What is your current height (in inches, without shoes)?" and, "What is your current weight (pre-pregnancy weight if pregnant)?" Self-reported waist circumferences were elicited by the question, "Please provide, to the best of your ability, your body circumference in inches." without further instruction. There are strong correlations between self-reported and clinically measured heights (r=0.96) and weights (r=0.96) [37], whereas self-reported waist circumferences are somewhat less precise, as indicated by their correlations with their clinical measurements (r=0.68) [37].

Distance run or walked was obtained from the question "Average miles run per week for:" and then listed the current and preceding five years with spaces for the responses. Pace was determined by the question "During your usual run, how many minutes does it take for you to run one mile?" Walking distance and pace were ascertained using the same questions for walking instead of running. Mileage for the baseline year was used for the analyses. Previously, we reported strong correlations between repeated questionnaires for self-reported running distance (r=0.89) [37]. To calculate MET-hours/wk for walking, we converted walking distance into duration (i.e., distance/mph) and calculated the average hours walked per week and the MET value for the reported pace [34,36]. Running MET values were calculated as 1.02 MET-hours per km [35]. Incident kidney cancer was provided by patient self-report. Incident kidney cancers were self-identified from the question "If you had a heart attack, stroke or cancer between 1991 and 2006, please complete the items in this box. a) Date of first cancer diagnosis (month/day/year): _____/ _____ / _____ b) Site (organ) of the cancer: _____. Sensitivity of self-reported malignant tumors is relatively high [3], and may be greater for kidney cancer diagnosis in this cohort given that surgery is the primary treatment and the cohort is generally well educated. Subjects were excluded for incident kidney cancer occurring within one-year of their baseline survey.

Statistical analyses were performed using the JMP statistical software package (SAS institute, Cary NC, version 5.1). Cox proportional hazard analyses were used to estimate the hazard ratio per MET-hours/wk run or walked. Results are presented as hazard ratios (risk reduction) and their percent reduction (calculated as 100*(hazard ratio-1)), and for categories of walking and running energy expenditure relative to falling short (<450 MET minutes per week =7.5 MET-hours/wk), achieving (450 to 750 MET minutes per week =7.5 to 12.5 MET-hours/wk), or exceeding the current recommendations by one to two-times (12.6 to 25.1 MET-hours/week), or by greater than two-times (≥25.2 MET-hours/wk) the current exercise recommendations [13]. Hazard ratios (HR) are presented along with their 95% confidence intervals (95%CI). All analyses were adjusted for age (age and age^2), sex, and cohort (first and second runners' cohorts, and walkers' cohort).

Results

Table 1 presents the characteristics of the subjects, divided by whether they fell below the current exercise recommendations for health (<7.5 MET-hours/wk), achieved the guideline exercise levels (7.5 to 12.5 MET-hours/wk), exceeded the guideline levels by 1- to 2-times (12.6 to 25.1 MET-hours/wk), or by ≥2-times that currently recommended (≥25.2 MET-hours/wk). Greater exercise energy expenditure was associated with being male, running (as compared to walking), fewer pack-years of cigarette use, less hypertension and diabetes medication use, greater alcohol intake, and greater leanness as measured by BMI and waist circumference. Because of the limited number of cases, runners and walkers were combined for the analyses of kidney cancer and adjusted for cohort, in addition to age and sex. Fifty-two incident kidney cancers were reported during the average 6.9-year follow-up (27 reported from National Runners' Health Study I, 9 from National Runners' Health Study II, and 16 from the National Walkers' Health Study). Only four patients specified renal vs. urothelial cell carcinoma; thus all kidney cancers were analyzed together without regard to type.

Running and walking

The age-, sex-, and cohort-adjusted risk for incident kidney cancer decreased on average 1.9% per MET-hours/week run or walked (HR: 0.981, 95%CI: 0.964 to 0.997, P=0.02). Compared to walking or running below guidelines levels, Table 2 shows that the risk for incident kidney cancer was reduced 61% by meeting the guidelines (P=0.07), 66.7% by running or walking 1- to 2-times the recommended levels (P=0.0005), and 76.2% by running or walking ≥2-times the recommended levels (P=0.005). The significant exercise-associated reductions in kidney cancer risk persisted when adjusted for baseline BMI, hypertension, diabetes, and pack-years of cigarette use in addition to the standard covariates. Further adjustment for alcohol intake and education had negligible effect on the risk reduction (not displayed). Relative to inadequate exercise, most of the apparent risk reduction occurred by achieving or exceeding the guideline activity levels.

Non-exercise effects

Table 3 displays the hazard ratios for incident kidney cancer vs. other baseline risk factors. Its risk increased on average 11.8% per kg/m^2 BMI. Compared to <22.5 kg/m^2, the risk for kidney cancer was 32.6% greater for 22.5 to 25 kg/m^2 (HR: 1.326, 95%CI: 0.600 to 3.022, P=0.49), 40.8% greater for 25 to 27.5 kg/m^2 (HR: 1.408, 95%CI: 0.553 to 3.509, P=0.46), 3.3-times greater for 27.5 to 30 kg/m^2 (HR: 3.309, 95%CI: 1.174 to 8.774, P=0.03), and 6.7-times greater for ≥30 kg/m^2 (HR: 6.692, 95%CI: 2.491 to 17.561, P=0.0003). Incident risk also increased 4.6% per cm in waist circumference (P=0.005), but not when adjusted for BMI. Subjects taking medications for blood pressure and diabetes at baseline were also at increased risk for kidney cancer (2.8- and 5.2-times that of nonusers, respectively). Cigarette use increased kidney cancer risk by 1.5% per pack-year (P=0.02). The associations of blood pressure and diabetes medications and cigarettes use with kidney cancer risk were diminished only slightly by BMI adjustment (P=0.04). Kidney cancer was unrelated to reported baseline intakes of red meat, fruit, and alcohol, and years of education. When adjusted for MET-hours/wk run or walked, the risk for incident kidney cancer continued to

increase significantly in association with pack-years of cigarette use and blood pressure and diabetes medication use, but not BMI

Discussion

These analyses suggest that failing to achieve the minimum guideline physical activity levels was associated with substantially greater risk for incident kidney cancer. Relative to exercising inadequately, the majority of the risk reduction was achieved by running or walking 7.5 to 12.5 MET-hours/week. Although there was little additional risk reduction at greater exercise energy expenditures, the broadness of the confidence intervals precludes asserting a precise dose-response relationship. Presumably, the 61% to 76% risk reduction mostly reflects reductions in the risk for renal cell carcinomas, although urothelial cell carcinomas of the renal pelvis have also been reported to decrease with physical activity [39].

The current results provides important additional evidence for a protective effect of physical activity given: 1) its prospective design, 2) strong significance when adjusted for other risk factors; and 3) significance for the sexes combined. A slight majority of the cohort and case-control studies report no significant risk reduction [5,10,12,14,18,20,25,26,27,30], including the multicenter International Renal Cell Cancer Study of 1,732 cases and their matched controls [21]. In at least one study, this may have been due to inadequate power (62% reduction adjusted for age, P=0.06, 54% reduction when further adjusted for BMI, hypertension, smoking [18]). One study actually reported a significant increase in risk with subjects who participated in hard leisure-time physical activity compared with less active subjects when adjusted for age, sex, smoking, BMI and hypertension (P=0.05 for trend) [5]. The case-control study by Chiu et al showed 60% lower odds for renal cell carcinoma in women when adjusted for hypertension, smoking, and possibly BMI [6]. Lindblad et al reported that compared to men of below average activity, the odds for renal cell cancer for very active men was significantly reduced by 48% for activity at age 30, and 63% for activity at age 40 when adjusted for age, education, smoking, and BMI [17]. Similarly, Menezes et al reported that when adjusted for age, BMI, and smoking, the highest quartile of total physical activity in men, and strenuous recreational physical activity in women, were at 51% and 59% lower odds for renal cell cancer than the lowest quartiles, respectively [22]. Neither Lindblad et al. nor Menezes et al adjusted for hypertension. The significant odds reduction reported by Tavani et al for occupational activity was eliminated by adjustment for education [29], and although the authors may be correct that this represented overadjustment, our own results remained significant when education was included as a covariate. Wilson et al.'s report of 42% to 65% reductions in the risk for urothelial cell carcinomas of the renal pelvis in several physically active job categories [39] may not be particularly germane to our result, given these cancers represent only about 6% of kidney cancers [1].

Among the remaining studies, two made no adjustments for BMI, hypertension, diabetes, or smoking [4,24]. The Iowa women's health study reported that vigorous intensity physical activity, but not moderate intensity activity, was predictive of age-adjusted incident kidney cancer risk (P=0.05) [24]. Given their reported 2.5-fold increase in risk associated with

obese vs. lean women, and 68% greater risk for hypertension, it is likely that additional adjustment for BMI and hypertension would have eliminated its significance. The authors of the Multiethnic cohort acknowledged that the significant association they report for women was possibly due to residual confounding by BMI, since the increase in renal cell cancer risk with increasing BMI was greater in women [28]. In the NIH-AARP Diet and Health Study, adjustment for BMI, smoking, hypertension, and diabetes reduced the risk reduction from 37% ($P \leq 0.01$) to 19% ($P=0.10$) for current exercise and sports, and from 28% ($P<0.01$) to 16% ($P=0.02$) for daily routine activity [23].

In our study, kidney cancer was based on self-reported physician diagnosis. We believe it unlikely that patients would be forgetful of its prior occurrence, or mistaken about undergoing treatment for kidney cancer. In support of its validity, our analyses showed the self-reported physician-diagnosed kidney cancer was significantly related to its other established risk factors: BMI, smoking, diabetes, and hypertension [7]. Consistent with other studies, we found no association between risk and alcohol intake, meat, or fruit [7].

Several limitations of the current analyses warrant attention. Self-report may under-represent the true incidence of kidney cancers due to affected individuals not responding to the follow-up questionnaire. In addition, since only nonfatal kidney cancers would be reported on follow-up surveys, it is not possible to determine to what extent the risk would be reduced for total (fatal and nonfatal) incident kidney cancers. However, 85% of those diagnosed with kidney cancer survive over 1 year and 71% survive over 5 years [1]. It is possible that higher-mileage runners and walkers receive better and more-timely treatment than those less active; however, diets high in fruits and low in meat, and higher educational attainment might also be associated with better and more timely health care access, and these factors were unrelated to incident kidney cancers. Finally we acknowledge that the National Runners' and Walkers' Health Study cohorts may not be representative of the general population, in particular, the generally high level of educational attainment of the cohort, and the small proportion of smokers at baseline suggests the cohort is healthier than the general population. The lower response rate for the walkers and the National Runners' Health Survey II may also affect generalizability of the findings. However, we do not expect that the etiology of kidney cancer in these runners and walkers would differ from that of the general population.

In conclusion, our results suggest that reduced risk for kidney cancer is an additional health benefit of regular exercise, and support the minimum guideline activity levels currently recommended [13]. Surveillance data show that the incidence of the disease appears to be plateauing after increasing over several decades [1]. Our analyses suggest that public health interventions to increase physical activity could substantially reduce incidence, particularly if the guidelines were promoted in terms of running and walking distances. The risk reduction and statistical significance reported here for 52 incident kidney cancers in 91,820 subjects are considerably greater than those achieved by the much larger NIH-AARP Diet and Health Study of 1,238 incident renal cell cancers in 482,386 subjects [23]. This may reflect the benefit of using a cohort study specifically designed to assess the health impact of physical activity in persons likely to maintain and be knowledgeable of their activity levels,

which does not combine every possible leisure-time activity, and which does not use a physical activity metric based on activity duration.

Acknowledgments

This research was supported by grant HL094717 from the National Heart, Lung, and Blood Institute and was conducted at the Ernest Orlando Lawrence Berkeley National Laboratory (Department of Energy DE-AC03-76SF00098 to the University of California). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Table 1

Baseline sample characteristics of the National Runners' and Walkers' Health Study participants (percent or mean±SD)

MET-hours/wk	<7.5	7.5 to 12.5	12.6 to 25.1	≥25.2
Sample size (N)	9380	6389	25516	50535
Males (%)	37.20	40.29	51.60	62.52
Walkers (number, (%))	4657 (49.65%)	3004 (47.02%)	5817 (22.80%)	2456 (4.86%)
Age (years)	49.96±13.92	48.93±13.18	47.01±12.03	44.04±11.13
Education (years)	15.82±2.60	16.11±2.56	16.33±2.47	16.34±2.45
Baseline smokers (number, (%))	334 (3.56%)	163 (2.55%)	505 (1.98%)	677 (1.34%)
Ex-smokers (number, (%))	3,344 (35.65%)	2,246 (34.74%)	9,224 (36.15%)	17,557 (35.15%)
Pack years smoked	5.61±14.41	4.88±12.67	5.20±12.64	4.87±11.96
Hypertensive medication users (number, (%))	1262 (13.51%)	665 (10.41%)	1865 (7.31%)	1922 (3.80%)
Diabetes medication users (number, (%))	255 (2.73%)	101 (1.58%)	251 (0.98%)	239 (0.47%)
Red meat (servings/d)	0.42±0.38	0.40±0.36	0.39±0.36	0.34±0.35
Fruit (pieces/d)	1.42±1.08	1.50±1.09	1.53±1.10	1.66±1.19
Alcohol (g/d)	5.96±10.46	6.71±10.63	8.14±11.82	8.47±12.53
BMI (kg/m^2)	25.74±5.20	24.81±4.13	23.83±3.26	22.68±2.62
Waist circumference (cm)	83.44±12.95	81.70±11.82	80.18±10.51	78.22±9.40

Men and women who were recruited between 1991 and 1993 (7.7 yr follow-up of 42,833 subjects) and between 1998 and 1999 (6.4 yr follow-up of 33,053 subjects) as part of the National Runners' Health Study and between 1998 and 1999 as part of the National Walkers Health Study (5.7 yr follow-up of 15,934 subjects). All trends significant at $P<10^{-15}$.

Table 2

Hazard ratios (95% confidence intervals) for incident kidney cancer by MET-hours/wk run or walked.

Exercise:	**Standard covariates***	**Standard covariates* and BMI.**	**Standard covariates*, BMI, blood pressure and diabetes medication use and pack-years of cigarette use.**
<7.5 MET-hours/wk 15 cases/9380 subjects	1.000	1.000	1.000
7.5 to 12.5 MET-hours/wk 4 cases/6389 subjects	0.390 (0.111, 1.077) P=0.07	0.428 (0.121, 1.188) P=0.11	0.429 (0.122, 1.191) P=0.11
12.6 to 25.1 MET-hours/wk 14 cases/25,516 subjects	0.333 (0.154, 0.715) P=0.005	0.352 (0.157, 0.784) P=0.01	0.352 (0.157, 0.786) P=0.01
≥25.2 MET-hours/wk 19 cases/50,535 subjects	0.238 (0.111, 0.522) P=0.0005	0.289 (0.131, 0.661) P=0.004	0.288 (0.130, 0.662) P=0.004

*Standard covariates include age (age, age^2), sex, and whether they were walkers or the 1st and 2nd recruitment of runners.

Table 3

Hazard ratios (95% confidence intervals) for incident kidney cancer.

	Each factor considered separately when adjusted for standard covariates*		All factors included simultaneously in the model, adjusted for exercise and standard covariates.
	No BMI adjustment	Adjusted for BMI	
BMI (per kg/m^2)	1.118 (1.047, 1.180) P=0.002		1.059 (0.984, 1.128) P=0.12
Waist circumference (per cm)	1.046 (1.015, 1.074) P=0.005	1.013 (0.965, 1.062) P=0.59	
Blood pressure medication use	2.784 (1.347, 5.454) P=0.007	2.456 (1.169, 4.905) P=0.02	2.208 (1.028, 4.487) P=0.04
Diabetes medication use	5.173 (1.508, 13.508) P=0.01	4.102 (1.166, 11.138) P=0.03	2.998 (0.829, 8.449) P=0.09
Smoking (pack-years)	1.015 (1.003, 1.025) P=0.02	1.013 (1.000, 1.023) P=0.04	1.012 (1.000, 1.021) P=0.04
Read meat (servings/d)	1.021 (0.448, 2.047) P=0.96	0.927 (0.397, 1.902) P=0.85	
Fruit (pieces/d)	0.938 (0.724, 1.169) P=0.60	0.969 (0.748, 1.198) P=0.80	
Alcohol (g/d)	0.989 (0.963, 1.010) P=0.34	0.988 (0.961, 1.010) P=0.31	
Education (years)	0.932 (0.841, 1.036) P=0.19	0.931 (0.839, 1.036) P=0.19	

*Adjusted for age (age, age^2), sex, and whether they were walkers or the 1st and 2nd recruitment of runners.