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Self-reported Intentional Weight Loss and Risk of Death in Moderate Chronic Kidney Disease in the United States

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Abstract

Objective: We hypothesized that intentional weight loss is associated with lower mortality risk, whereas unintentional weight loss is associated with higher mortality risk in chronic kidney disease (CKD).

Design and Methods: We examined this hypothesis in 872 participants with age >20 years, body mass index ≥ 25 kg/m² and CKD from 1999–2004 National Health and Nutrition Examination Survey who reported their 1 year prior and current weights and the intent to lose weight. We examined the association of self-reported intentional versus unintentional weight loss with all-cause mortality. Participants with no intent to lose weight and no change in weight were the reference group. A multivariable Cox regression model was used to relate mortality with intentional and unintentional weight losses after adjustment for demographics and comorbidity.

Results: There were 446 deaths over 6271 years of follow-up. Compared to the reference group, intentional weight loss of 5% to <10% (hazard ratio (HR) 1.22, 95% confidence interval (CI): 0.74–1.99), intentional weight loss of $\geq 10\%$ (HR 1.53, 95% CI: 0.75–3.12), and unintentional weight loss of 5% to <10% (HR 1.11, 95% CI: 0.71–1.75) were not associated with mortality; however, unintentional weight loss of $\geq 10\%$ (HR 1.66, 95% CI: 1.06–2.58) was significantly associated with higher risk of mortality. Retrospective design and self-reported weight loss were the limitations.

Conclusions: Intentional weight loss in CKD participants was not associated with lower mortality risk. This might reflect residual confounding. Mechanistic and interventional studies are warranted to determine the effects of intentional weight loss in CKD.

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Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1053/j.jrn.2018.04.001>.

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Introduction

OBESITY IS CONSIDERED one of the risk factors for the development and progression of chronic kidney disease (CKD).¹⁻³ Both experimental and population studies have found mechanistic link between obesity and CKD independent of diabetes and hypertension.⁴

In general population, weight loss results in improvement in risk factors for cardiovascular disease, quality of life, glycemic control, and other obesity-related coexisting illnesses.⁵ However, the impact of weight loss on the risk of all-cause mortality and cardiovascular disease is not clear perhaps because of confounding from unintentional weight loss or methods used for weight loss.⁶⁻¹⁰ Given the mechanistic link between obesity and CKD, it is intuitive to consider the beneficial effect of intentional weight loss in CKD patient's outcomes. In early CKD participants, weight loss achieved by various interventions including diet, exercise, lifestyle changes, pharmacologic treatment, and bariatric surgery have improved proteinuria and albuminuria, and normalized GFR, particularly if achieved by surgical interventions.¹¹ However, there is very limited data evaluating the effect of weight loss on hard outcomes in CKD patients. A small nonrandomized observation study in patients with CKD and BMI >30 or >28 kg/m² with comorbidities reported a longer event-free (death, myocardial infarction, stroke, and heart failure hospitalization) time over median follow-up of 32 months in the group who followed a 12-month weight loss program. The authors reported that participation in the weight loss program rather than weight loss alone was associated with longer event-free survival.¹² Nonetheless, there is no large study evaluating the effect of weight loss on mortality in community dwelling population with CKD.

We hypothesized that intentional weight loss is associated with lower risk of mortality, whereas unintentional weight loss is associated with increased risk of mortality in CKD and examined this hypothesis in the 1999–2004 National Health and Nutrition Examination Survey (NHANES) data set.

Materials and Methods

Study Population

The National Center for Health Statistics is conducting NHANES to obtain a sample of a representative population of the noninstitutionalized United States population. In the 1999–2004 NHANES data set, there were total of 8802 subjects who were 20 years and had BMI 25 kg/m². Of these, weight loss and estimated glomerular filtration rate (eGFR) data were available in 8245 subjects. CKD was defined as estimated CKD-EPI eGFR <60 mL/minute/1.73 m².¹⁴ The final cohort included 872 individuals who had CKD and in whom mortality statistics were available (Fig. 1).

Baseline Data

NHANES data collection details have been published elsewhere.¹³ Weight history obtained in this survey included the following questions: (1) How much do you weigh without clothes and shoes? (2) How much did you weigh a year ago? and (3) for those with >10 lb weight loss: Was the change between your current weight and weight a year ago intentional?

Regardless of the weight change, all participants were asked whether they tried to lose weight in the past 12 months.

In the current analysis, the reference group comprised of participants who did not intend to lose weight and with no weight change (the difference between past year weight and current weight was between -5% and $+5\%$). Weight gain group was defined as those who had 5% gain. Participants who reported an intention to lose weight were categorized further based on the degrees of weight loss as no weight change (between -5% and $+5\%$), 5% to $< 10\%$ weight loss, and 10% weight loss. Unintentional weight loss groups (those who did not report an intention to lose weight but lost $> 5\%$ weight) were categorized into 5% to $< 10\%$ loss and 10% weight loss. In sensitivity analyses, similar weight change groups were defined using 10 to < 20 lbs and 20 lbs absolute weight loss.

Mortality Data

A Linked Mortality File through December 31, 2011 was created by the National Center for Health Statistics using a probabilistic match between NHANES and death certificate records from the National Death Index.¹⁵

Statistical Analysis

NHANES is based on a complex probability sample design. We used the svy suite of commands in Stata software, version 13 (Stata Corp., College Station, TX) and followed the analytical guidelines for NHANES data proposed by the Centers for Disease Control and Prevention. Hence, all results take survey weights into account.

Descriptive statistics were obtained for weight change groups including means and standard deviations (SDs) for numeric variables and proportions for categorical variables.

A multivariable Cox regression model was used to relate mortality with weight gain, intentional and unintentional weight loss groups. The reference group comprised of participants who did not intend to lose weight and with no weight change (the difference between past year weight and current weight was between -5% to $+5\%$). The first model was adjusted for pre-BMI, baseline demographics (age, gender, race, education level), smoking, and alcohol use. The second model was further adjusted for comorbid conditions (myocardial infarction, congestive heart failure, stroke, lung disease, cancer, diabetes, and hypertension) and eGFR, which are potential confounders as well as intermediate variables in the causal pathway between weight loss and mortality.

These analyses were repeated with absolute weight (in lbs) change categories.

All analyses were performed with svy suite in Stata 14 (STATA Corporation, College Station, Texas).

Results

Baseline characteristics of 872 participants categorized by the 7 weight change categories are presented in Table 1. Supplemental table 1 presents similar data for the weight change in

lbs. The reference category of no intent to lose weight and no weight change, by definition had stable BMI ($29.6 \pm 4.1 \text{ kg/m}^2$ a year ago and $29.6 \pm 4.2 \text{ kg/m}^2$ at baseline). Weight gain group had a mean weight gain of 19.5 ± 9.4 lbs, and the BMI increased from $31.1 \pm 3.9 \text{ kg/m}^2$ to $34.4 \pm 4.6 \text{ kg/m}^2$. Those who intended to lose weight but did not lose weight had a modest -0.5 ± 3.6 lb change. However, those who intended to lose weight and lost weight between 5 to <10% and 10% had average weight losses of -15.0 ± 5.4 lbs and -33.6 ± 15.0 lbs, respectively. The unintentional weight loss groups also had comparable weight losses of -12.4 ± 3.8 lbs and -36.0 ± 16.1 lbs in the 5 to <10% and 10% weight loss groups, respectively.

Higher pre-BMI, age, and high school education were significantly associated with intent to lose weight in unadjusted logistic regression models, but only higher pre-BMI and age remained significant in a multivariate logistic regression model (Table 2).

There were 446 deaths over 6271 years of follow-up. The number of deaths and the death rate in the weight change groups are provided in Figure 2. The mortality rate was the highest in the unintentional weight loss group irrespective of degree of weight loss.

Compared to the reference group (no intent to lose weight and no change in weight), in a multivariate Cox regression model (Fig. 2, panel A) adjusted for pre-BMI, age, gender, race, smoking, and alcohol use, weight gain group had a nonsignificantly higher hazard of death (HR 1.29, 95% CI: 0.84–1.98). Compared to the reference group, HR for mortality in the intent to lose weight but no weight change group, intent to lose weight with 5 to <10% weight loss group, and intent to lose weight with 10% weight loss group were 0.97 (95% CI: 0.72–1.32), 1.33 (95% CI: 0.83–2.13), and 1.87 (95% CI: 0.99–3.55), respectively. With adjustment for factors that are potential confounders as well as intermediate variables, these associations attenuated further (Fig. 2, panel B).

In contrast, unintentional weight loss of 10% was significantly associated with increased mortality risk in both models (Fig. 2, panels A and B).

When analyses were repeated with weight loss defined as lbs, the pattern of results were similar (Fig. 3, panels A and B) for both intentional and unintentional weight losses.

Discussion

Among a nationally representative sample of US adults with CKD, unintentional weight loss 10% associated with higher risk of mortality. Contrary to our hypothesis, the intentional weight loss did not associate with lower risk of mortality in the CKD subpopulation.

In obese persons, alterations in the adipokines produced by adipose tissue result in metabolic derangements like insulin resistance, dyslipidemia, hypertension, and inflammation.¹⁶ Hence, higher body size in the general population has been associated with increased mortality.¹⁷ Although intentional weight loss in type 2 diabetes in the LOOK-AHEAD trial did not result in lower cardiovascular risk,⁸ a meta-analysis of randomized controlled trials of weight loss in the general population suggested a 15% decrease in mortality with intentional weight loss.¹⁸

However, the association of obesity with mortality in CKD population is not very straightforward. An analysis of Atherosclerosis Risk in Communities Study participants with CKD showed in those participants with BMI < 25 kg/m², higher BMI was associated with lower risk of mortality.¹⁹ In contrast, no association was noted between BMI and mortality in participants with CKD and BMI of 25 kg/m² or greater.¹⁹ In additional analysis, Madero et al²⁰ also reported no association between sex-specific BMI quartiles and all-cause or cardiovascular mortality after a median follow-up of 10 years in 1,759 participants with mean age of 51 years and eGFR of 39 ± 21 mL/minute/1.73 m² in the Modification of Diet in Renal Disease Study. In an analysis of US veterans,²¹ BMI <25 kg/m² were associated with worse outcomes in all patients, independent of severity of CKD, but BMI 35 kg/m² were associated with worse outcomes in patients with earlier stages of CKD, but this association was attenuated in those patients with eGFR<30 mL/minute/1.73 m².

In a meta-analysis of observational and interventional studies of weight loss in CKD suggested that weight loss achieved by nonsurgical intervention is associated with significant improvement in proteinuria, and weight loss achieved by bariatric surgery in morbidly obese subjects is associated with normalization of glomerular hyperfiltration.¹¹ In contrast, observational cohort studies reported increased risk of mortality with weight loss in CKD patients prior to initiation of dialysis²² and in patients on chronic maintenance dialysis.^{23–26} These observational studies of weight loss in CKD and dialysis patients are limited by the lack of data on whether the weight loss was intentional or unintentional,^{27,28} as unintentional weight loss might reflect an underlying comorbidity such as cancer or severe intercurrent illness.

Therefore, we conducted this analysis of NHANES data, which offers a unique opportunity to study mortality associations of intentional and unintentional weight loss in overweight or obese participants with CKD. Unintentional weight loss 10% or 20 lbs is associated with increased mortality risk.

On the other hand, intentional weight loss 10% or 20 lbs appears to associate with increased mortality risk with adjustment for pre-BMI, demographics, smoking, and alcohol use. However, with adjustment for comorbid conditions, these associations attenuated and reached nonsignificance. Nonetheless, contrary to our hypothesis, we did not note a lower risk of mortality with intentional weight loss in the CKD population. There are several possible explanations for these findings. First, these results could be because of confounding due to indication, that is, those who lose weight intentionally might have underlying (unmeasured) reasons that resulted in the intent to lose weight. While we tried to account for this with multivariable models, residual confounding cannot be excluded. Second, the methods used to achieve weight loss might influence mortality risk.^{8,29} A previous report suggested that a significant proportion of the CKD population use diets that may have high protein content and medications to promote weight loss that may be harmful.³⁰ Third, weight loss might have resulted in significant loss of not only fat but also muscle which might increase the risk for death. A small nonrandomized observation study¹² in patients with CKD and BMI >30 or >28 kg/m² with comorbidities, patients assigned to 12-month structured weight loss program lost significantly more weight compared to control group and sustained a longer event-free (death, myocardial infarction, stroke and heart failure

hospitalization) time over median follow-up of 32 months. However, on further analysis, it was the participation in the weight loss program which helped with the muscle mass, rather than weight loss alone which associated with longer event-free survival. Fourth, it could be speculated that catabolic pathways involved in weight loss might be harmful in those with CKD, but there is no evidence to support that notion at this time.

There were some important limitations to our study. First, the retrospective observational nature of the study precludes drawing any causal inferences. Multivariate models might not eliminate residual confounding. Second, weight loss and intent to lose weight were self-reported. It is conceivable that some with unintentional weight loss “claimed credit” by stating that weight loss was intentional. Third, most of the participants with CKD in NHANES reflect stage III CKD and not more advanced CKD.

Conclusion

Unintentional weight loss in overweight/obese participants is associated with increased mortality risk in CKD population. The observation that intentional weight loss in CKD participants was not associated with lower mortality risk warrants further mechanistic and interventional studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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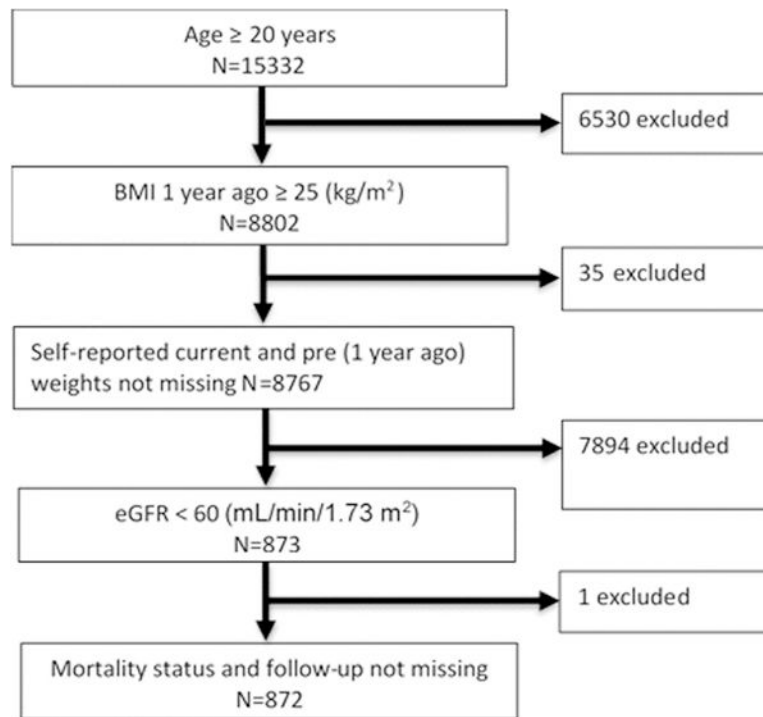


Figure 1. Flow chart of participant inclusion criteria. eGFR, estimated glomerular filtration rate.

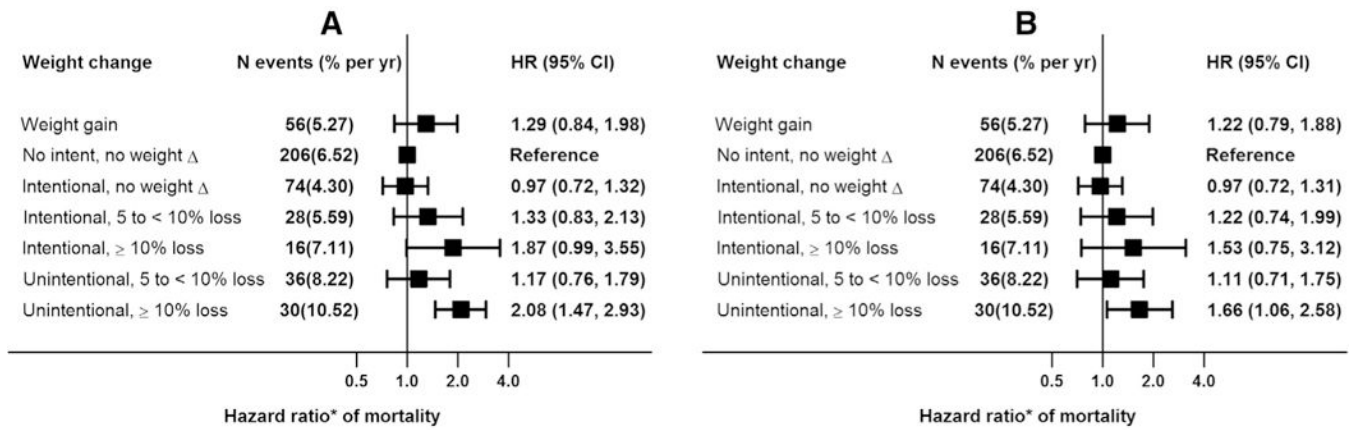
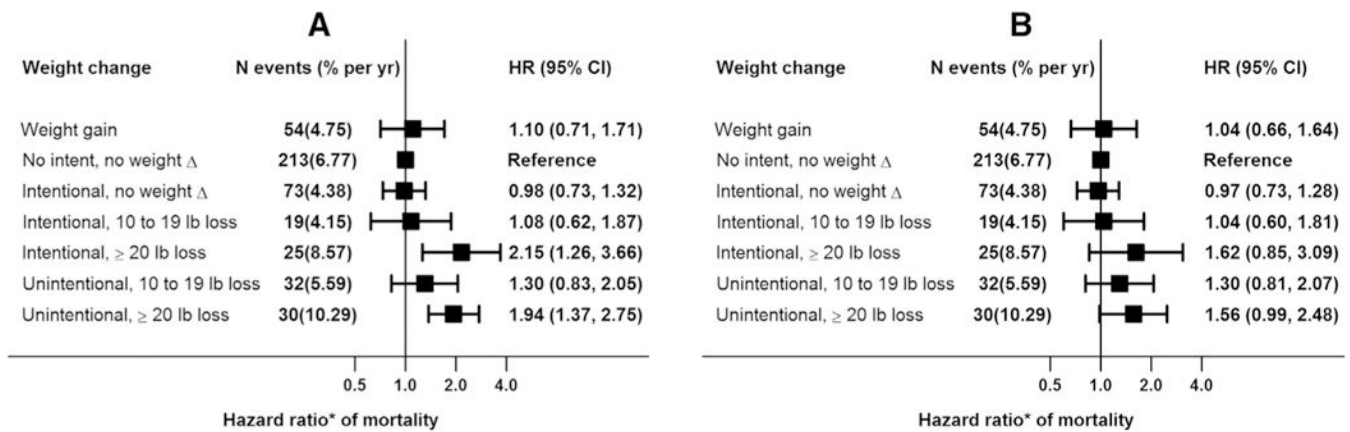


Figure 2. Mortality associations of intentional or unintentional weight loss (%) in CKD subpopulations. (A) Model 1 adjusted for pre-BMI, age, gender, race, smoking, alcohol and education; (B) Model 1 plus myocardial infarction, congestive heart failure, stroke, diabetes, hypertension, eGFR, lung disease and cancer. CKD, chronic kidney disease.

**Figure 3.**

Mortality associations of intentional or unintentional weight loss (lb) in CKD subpopulations. (A) Model 1 adjusted for pre-BMI, age, gender, race, smoking, alcohol and education; (B) Model 1 plus myocardial infarction, congestive heart failure, stroke, diabetes, hypertension, eGFR, lung disease and cancer. CKD, chronic kidney disease; BMI, body mass index; eGFR, estimated glomerular filtration rate.

Table 1.
Baseline Characteristics of CKD Participants by % Weight Change Groups (N = 872)

Variable	No Intent to Lose Weight, Weight, No Weight Δ		Intent to Lose Weight		Unintentional Weight Loss		
	N = 117	N = 383	No Weight Δ	5 to <10% Loss	10% Loss	5 to <10% Loss	10% Loss
	14.7%	39.8%	23.1%	7.7%	4.5%	5.5%	4.7%
Weight change (lb)	19.5 \pm 9.4	0.1 \pm 3.0	-0.5 \pm 3.6	-15.0 \pm 5.4	-33.6 \pm 15.0	-12.4 \pm 3.8	-36.0 \pm 16.1
Weight change (%)	10.6 \pm 5.1	-0.02 \pm 1.63	-0.2 \pm 1.9	-7.2 \pm 1.1	-16.4 \pm 6.4	-7.0 \pm 1.6	-18.2 \pm 6.8
BMI 1 y ago (kg/m ²)	31.1 \pm 3.9	29.6 \pm 4.1	31.0 \pm 4.1	34.4 \pm 7.6	33.8 \pm 4.5	30.1 \pm 4.7	32.6 \pm 4.9
Baseline BMI (kg/m ²)	34.4 \pm 4.6	29.6 \pm 4.2	30.9 \pm 4.1	31.9 \pm 6.9	28.2 \pm 4.1	28.0 \pm 4.3	26.6 \pm 4.1
Age (y)	66.9 \pm 12.5	74.6 \pm 9.6	68.8 \pm 10.3	66.4 \pm 11.0	68.2 \pm 8.2	77.3 \pm 9.1	72.3 \pm 11.1
Male (%)	32.6	48.7	46.1	33.4	28.8	39.4	29.5
African-American race (%)	10.9	6.6	7.1	10.6	12.3	17.5	19.1
Smoking (%)	56.5	47.5	51.6	46.5	36.0	45.1	38.7
Alcohol use (%)	48.1	54.0	53.7	49.1	42.8	39.6	30.6
High school education (%)	66.9	62.4	75.1	73.2	62.3	48.2	46.6
Diabetes (%)	23.8	27.0	25.9	33.0	44.4	20.2	24.2
Hypertension (%)	74.2	77.8	73.4	71.7	85.9	79.8	71.7
Myocardial infarction (%)	16.3	17.4	14.4	21.4	18.9	9.2	15.7
Congestive heart failure (%)	16.7	13.1	6.3	20.9	22.4	13.2	25.0
Stroke (%)	14.1	10.9	7.7	15.2	24.9	12.9	8.0
Lung disease (%)	16.6	10.3	12.4	22.4	13.2	12.9	18.0
Cancer (%)	20.6	25.8	21.8	25.1	18.2	19.3	6.3
eGFR (mL/min/1.73 m ²)	46.4 \pm 10.8	48.1 \pm 10.6	48.3 \pm 8.9	48.8 \pm 9.1	46.9 \pm 10.4	45.3 \pm 12.3	42.4 \pm 15.5

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Table 2.

Associations of Baseline Factors With Intention to Lose Weight

Clinical Factors	Odds Ratio of Intent to Lose Weight (95% CI and P Value)	
	Unadjusted	Multivariate Model
BMI 1 y ago (for each 1 kg/m ²)	1.08 (1.03 to 1.12, .001)	1.06 (1.01 to 1.11, .01)
Age (for each 5 y)	0.84(0.75 to 0.94, .003)	0.87 (0.77 to 0.98, .03)
Male	0.93(0.64 to 1.35, .71)	0.87 (0.58 to 1.31, .51)
African–American race	0.90 (0.63 to 1.28, .54)	0.82 (0.53 to 1.26, .35)
Smoking	0.99 (0.71 to 1.39, .97)	0.96 (0.65 to 1.41, .82)
Alcohol use	1.06(0.75 to 1.50, .72)	1.03 (0.72 to 1.47, .89)
High school education	1.73 (1.11 to 2.70, .02)	1.61 (0.97 to 2.66, .06)
Diabetes	1.24 (0.87 to 1.77, .23)	1.26 (0.86 to 1.85, .23)
Hypertension	0.89 (0.59 to 1.36, .59)	0.86 (0.56 to 1.33, .48)
Myocardial infarction	1.01 (0.61 to 1.68, .97)	1.25 (0.66 to 2.36, .48)
Congestive heart failure	0.75 (0.50 to 1.13, .17)	0.66 (0.41 to 1.07, .09)
Stroke	1.00 (0.51 to 1.94, .99)	1.20 (0.59 to 2.42, .61)
Lung disease	1.21 (0.69 to 2.12, .51)	1.19 (0.62 to 2.29, .60)
Cancer	0.97 (0.63 to 1.48, .87)	1.14 (0.73 to 1.77, .55)