Practice of Epidemiology

Simultaneous Association of Total Energy Consumption and Activity-Related Energy Expenditure With Risks of Cardiovascular Disease, Cancer, and Diabetes Among Postmenopausal Women

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Total energy consumption and activity-related energy expenditure (AREE) estimates that have been calibrated using biomarkers to correct for measurement error were simultaneously associated with the risks of cardiovascular disease, cancer, and diabetes among postmenopausal women who were enrolled in the Women's Health Initiative at 40 US clinical centers and followed from 1994 to the present. Calibrated energy consumption was found to be positively related, and AREE inversely related, to the risks of various cardiovascular diseases, cancers, and diabetes. These associations were not evident in most corresponding analyses that did not correct for measurement error. However, an important analytical caveat relates to the role of body mass index (BMI) (weight (kg)/height (m)^2). In the calibrated variable analyses, BMI was regarded, along with self-reported data, as a source of information on energy consumption and physical activity, and BMI was otherwise excluded from the disease risk models. This approach cannot be fully justified with available data, and the analyses herein imply a need for improved dietary and physical activity assessment methods and for longitudinal self-reported and biomarker data to test and relax modeling assumptions. Estimated hazard ratios for 20% increases in total energy consumption and AREE, respectively, were as follows: 1.49 (95% confidence interval: 1.18, 1.88) and 0.80 (95% confidence interval: 0.69, 0.92) for total cardiovascular disease; 1.43 (95% confidence interval: 1.17, 1.73) and 0.84 (95% confidence interval: 0.73, 0.96) for total invasive cancer; and 4.17 (95% confidence interval: 2.68, 6.49) and 0.60 (95% confidence interval: 0.44, 0.83) for diabetes.

body mass index; cancer; cardiovascular disease; diabetes; energy consumption; hazard ratio; measurement error; physical activity

Abbreviations: AREE, activity-related energy expenditure; BMI, body mass index; CVD, cardiovascular disease; FFQ, food frequency questionnaire; MET, metabolic equivalents; NPAAS, Nutrition and Physical Activity Assessment Study; TEC, total energy consumption; WHI, Women's Health Initiative; WHIOS, Women's Health Initiative Observational Study.

Diet and physical activity patterns over the lifespan constitute exposures that could explain much of the dramatic variation in chronic disease incidence rates worldwide (1), while also contributing importantly to risk variations within populations. Studies of migrants suggest that recent exposures, when markedly different from those prior to migration, may be particularly influential (2). Yet, decades of intensive analytical epidemiology research (3, 4) have failed to identify specific diet and activity factors that explain much of the variation in chronic disease risk. This lack of evidence undermines public health recommendations regarding diet and physical activity and may detract from needed public health policy initiatives.

In cohort study settings, the use of objective consumption biomarkers, in conjunction with self-reported dietary data,

provides a practical approach to strengthening nutritional epidemiology research that has previously relied on self-reported diet data without meaningful correction of measurement error. Recently, we used this biomarker calibration approach in cohorts of the Women's Health Initiative (WHI) to study total energy consumption (TEC) and protein consumption in relation to the risk of cardiovascular diseases (CVDs) (5), cancers (6), and diabetes (7), along with several other clinical outcomes (8–11). These applications rely on a nutrient biomarker study (12) within the WHI dietary modification trial cohort and a Nutrition and Physical Activity Assessment Study (NPAAS) (13) within the Women's Health Initiative Observational Study (WHIOS) cohort. They revealed (5–11) multiple significant disease risk associations, most of which were not evident without correction for measurement error. Most of the TEC associations, however, were no longer evident when body mass index (BMI) (weight (kg)/height (m)^2) was added to the disease risk model.

The regression calibration approach (14–16) in these WHI analyses used equations that were developed by using linear regression of log-transformed consumption biomarker values on corresponding log-transformed self-reported values and other study subject characteristics. The calibration equations allow measurement error–corrected consumption estimates to be calculated throughout study cohorts for use in disease association analyses. Calibration equations have been developed using a doubly labeled water biomarker and a 24-hour urinary nitrogen excretion biomarker for TEC and protein consumption, respectively, and for their ratio (12, 13).

Although less studied, the use of objective markers presumably has similar potential to strengthen the methodology of physical activity epidemiology. An objective measure of total activity-related energy expenditure (AREE) was obtained in the NPAAS by subtracting resting energy expenditure (assessed by indirect calorimetry) from the doubly labeled water estimate (12, 13) of TEC. Calibration equations for AREE were developed in the NPAAS by linear regression of the log-transformed total AREE biomarker on log-transformed self-reported estimates of total AREE and on other study subject characteristics (17). These equations can be used to develop measurement error–corrected estimates of AREE throughout the observational study cohort.

The calibration equations just mentioned include BMI in the equations for both TEC and AREE. It is well recognized that BMI can provide a valuable source of information on long-term TEC and AREE, as well as associated energy balance. For example, a 1997 review of food, nutrition, and cancer prevention included the statement, "In the view of the panel, the effect of energy intake on cancer is best assessed by examining the data on related factors: rate of growth, body mass, and physical activity" (18, p. 171). We will return to this topic in the Methods and Discussion sections.

This article explores both the substantive issue of simultaneous association of TEC and AREE with the risk for major chronic diseases under certain assumptions, as well as the methodological issue of study designs and data collection approaches that may be able to strengthen analyses of these important associations in future studies.

METHODS

The WHI Observational Study

The design of the WHIOS has been presented previously (19–21). The analyses presented here are based on data from the WHIOS, which enrolled 93,676 postmenopausal women ranging in age from 50 to 79 years at 40 US clinical centers during 1993–1998. Women who had an estimated survival time of less than 3 years were excluded. Women in the WHIOS completed a WHI food frequency questionnaire (FFQ) as part of the enrollment process. The FFQ collects data on frequency of intake and portion sizes for 122 foods and food groups during the past 3 months. It also includes 19 adjustment questions that focus on dietary fat, as well as 4 summary questions (22). Dietary data were analyzed for nutrient content using the University of Minnesota's Nutrition Database for Research (www.ncc.umn.edu).

Observational study participants completed a baseline WHI personal habits questionnaire. This is a short, self-administered questionnaire that inquires about the usual frequency and duration of walking activity outside the home, as well as other mild, moderate, or strenuous recreational activities (23). Standard intensity values (24), expressed as metabolic equivalent units (METs), were assigned to each activity, multiplied by reported durations, and summed to compute AREE in MET-hours per week. Because the personal habits questionnaire focuses on recreational activity, other WHI questionnaires were used to obtain MET estimates for housework, yard work, sitting, sleeping, and all other activities, and the activity sources were combined to produce total daily AREE estimates (17). METs were assigned to each of the activity categories using standard algorithms (24).

Nutrition and Physical Activity Assessment Study

During 2007–2009, the NPAAS enrolled 450 postmenopausal women with stable weight from the WHIOS (13). Women were recruited from WHIOS enrollees at 9 WHI clinical centers. Black and Hispanic women were oversampled, as were women with extreme BMI values and relatively younger postmenopausal women. Women were excluded from the NPAAS for weight instability in the preceding months or travel plans during the study period. A 20% reliability subsample repeated the entire biomarker study protocol approximately 6 months after the original protocol application.

The NPAAS protocol (13, 17) involved 2 clinical center visits separated by a 2-week period, along with at-home activities. The first visit included eligibility confirmation; informed consent; measured height and weight using a standardized protocol; doubly labeled water dosing for short-term energy expenditure assessment; and completion of a FFQ, a dietary supplement questionnaire, a personal habits questionnaire, and other questionnaires needed for the assessment of AREE. The first visit also included collection of a blood specimen and spot urine samples after doubly labeled water dosing. Participants collected 24-hour urine samples on the day prior to the second clinic visit. At the second clinic visit, the 24-hour urine samples were delivered to clinic staff, participants provided additional spot urine samples and a fasting blood sample, and indirect calorimetry was

Table 1. Baseline Characteristics for Women in the Women's Health Initiative Observational Study, Enrolled During 1994–1998, and in the Nutrition and Physical Activity Assessment Study, Enrolled During 2007–2009

Characteristic	WHIOS		NPAAS	
	%	No.	%	No.
Age, years				
<50–59	31.7	29,710	67.6	304
60–69	44.0	41,200	26.4	119
≥70	24.3	22,766	6.0	27
Body mass index[a]				
<25.0 (Normal)	40.3	37,796	39.8	179
25.0–29.9 (Overweight)	33.6	31,462	23.6	106
≥30.0 (Obese)	24.9	23,313	36.7	165
Race/ethnicity				
White	83.3	78,016	64.0	288
Black	8.2	7,635	18.7	84
Hispanic	3.9	3,609	14.2	64
Other	4.4	4,151	3.1	14
Income (annual household)				
<$20,000	15.0	14,018	9.6	43
$20,000–$34,999	21.6	20,226	20.4	92
$35,000–$49,999	18.6	17,430	18.7	84
$50,000–$74,999	18.7	17,487	21.8	98
≥$75,000	18.8	17,608	26.0	117
Educational level				
Less than high school diploma	5.2	4,849	3.6	16
High school diploma/GED	16.1	15,122	10.7	48
School after high school	36.2	33,935	34.9	157
College degree or higher	41.6	39,003	50.2	226
Smoking				
Current	6.2	5,790	4.7	21
Past	42.2	39,514	39.8	179
Never	50.2	47,021	54.4	245
Alcohol intake, drinks/week				
≥7	12.5	11,704	11.1	50
1–7	25.4	23,824	30.2	136
<1	31.4	29,431	32.2	145
Past	18.7	17,555	15.3	69
Never	11.2	10,477	11.1	50

Table continues

conducted. Total energy expenditure (and hence TEC for weight-stable persons) was estimated from relative urinary elimination rates of oxygen-18 and deuterium over the 2-week protocol (25).

Resting energy expenditure was estimated (17) by indirect calorimetry using a standard protocol (26). Metabolic carts were calibrated each day, and gasses were monitored during each test. Participants arrived after a 12-hour fast and rested in a semireclined position in a thermally neutral room for 30 minutes followed by a 30-minute test. Data from the first 10 minutes were excluded on the basis of time needed

to achieve steady-state metabolism (26). Participants who did not reach a steady state or who did not have at least 10 minutes of useable data (*n* = 16) were not included in AREE biomarker analyses. The AREE biomarker was defined as total energy expenditure from doubly labeled water minus resting energy expenditure.

Outcome ascertainment and categories

Clinical outcomes were reported annually by self-administered questionnaire in the WHIOS (27). The initial CVD or

Table 1. Continued

Characteristic	WHIOS		NPAAS	
	%	No.	%	No.
Recreational physical activity, METs/week				
<1.5	17.5	16,364	12.4	56
1.5–6.2	20.3	19,062	19.8	89
6.3–14.7	25.6	23,942	27.8	125
≥14.8	35.5	33,257	39.3	177
Personal history				
Cardiovascular disease	20.7	19,425	14.9	67
Cancer	13.9	13,037	14.0	63
Treated for diabetes	4.2	3,902	0.2	1
Family history				
Cardiovascular disease	66.4	62,242	61.6	277
Cancer	47.3	44,279	45.6	205
Diabetes	31.4	29,403	30.4	137
Hypertension	33.2	31,074	22.9	103
Postmenopausal hormone usage				
Current	44.4	41,630	49.8	224
Never	40.6	38,024	38.0	171
Past	14.9	13,937	12.2	55
Self-reported energy measures				
TEC	1,416[b]	547,3071[c]	1,457[b]	541,3289[c]
AREE	629[b]	249,1268[c]	631[b]	242,1338[c]
Calibrated energy measures				
TEC	2,162[b]	1775,2740[c]	2,264[b]	1866,2813[c]
AREE	872[b]	570,1377[c]	992[b]	636,1494[c]

Abbreviations: AREE, activity-related energy expenditure; GED, general educational development; MET, metabolic equivalent; NPAAS, nutrition and physical activity assessment study; TEC, total energy consumption; WHIOS, Women's Health Initiative Observational Study.

[a] Weight (kg)/height (m)^2.
[b] Expressed as geometric mean.
[c] Expressed as 95% confidence interval.

invasive cancer event during WHIOS follow-up was confirmed by physician adjudicators who reviewed medical records and pathology reports at local clinical centers. Additionally, coronary heart disease, stroke, and all deaths were centrally reviewed by expert committees, and all cancers except nonmelanoma skin cancer were centrally coded using the National Cancer Institute's Surveillance, Epidemiology, and End Results system (27). Centrally adjudicated data were used when available; otherwise, locally adjudicated outcomes were used.

CVD categories included those previously considered in relation to TEC (5), along with congestive heart failure. Cancer categories included those previously considered (6), along with an "obesity-related cancer" category. Obesity-related cancer was defined as combined breast, colon, rectal, endometrial, and kidney cancers, though there are other cancers for which there is some evidence for an obesity association (4).

Prevalent diabetes at baseline was self-reported during eligibility screening. Incident diabetes during follow-up was documented by self-report at each annual contact. Data from a WHI Diabetes Confirmation Study showed these self-reports to be consistent with medication inventories of oral antidiabetes agents or insulin (28).

At the end of the planned WHI program time period (in April 2005), women were invited to reenroll for an additional nonintervention follow-up, and more than 80% of women chose to do so. The CVD and cancer association analyses presented here include WHIOS follow-up through September 30, 2010. The diabetes analyses include follow-up through September 17, 2012.

Statistical analyses

For analysis of TEC and AREE in relation to clinical outcomes, we used the Cox regression model (29) with the same potential confounding variables as in previous analyses of TEC in relation to these outcomes (5–7). Specifically, for CVD outcomes, such variables included age (linear), race/ethnicity,

family income, education, history of cigarette smoking, alcohol consumption, prior menopausal hormone use, hypertension, CVD in a first-degree relative, personal history of cancer, and personal or family history of diabetes. The "total invasive cancer" category included these same potential confounding variables, exclusive of prevalent CVD and family history of CVD or diabetes. Diabetes analyses included the same control variables as did the CVD analyses, except family history of CVD, while including personal history of CVD. Full details on the potential confounding variables included in each analysis are given in Web Table 1, available at http://aje.oxfordjournals.org/. Missing data rates were generally low for modeled variables, and study subjects were excluded from analyses for a particular outcome if any of the corresponding modeled covariates was missing. Women having prior CVD, prior invasive cancer, or prior treated diabetes at enrollment were excluded from respective CVD, cancer, and diabetes analyses.

The Cox models were stratified on age at baseline in 5-year categories. For each outcome category, the disease occurrence time for cases was defined as days from WHIOS enrollment to diagnosis, and censoring time for noncases was defined as days from enrollment to the earlier of the date of last follow-up contact or September 30, 2010, for CVD and cancer outcomes or September 17, 2012, for diabetes. Log-TEC and log-AREE, with or without measurement error calibration, along with potential confounding variables, were included in the Cox model log-hazard ratio, thereby specifying a constant hazard ratio for a fractional increase in TEC or AREE. Standard errors for hazard ratios from analyses that included calibrated exposures used a bootstrap estimation procedure with 1,000 bootstrap samples to acknowledge random variation in calibration equation coefficient estimates.

TEC and AREE calibration equations, which update those previously published, were developed by linear regression of log-transformed biomarker values on log-transformed self-reported TEC and AREE, along with BMI and all variables in the disease risk model for the outcome in question, in accordance with standard regression calibration methodology (14–16).

The hazard ratio analyses are conceptualized as targeting usual TEC and AREE over a lengthy time period of years or even decades. Denote the corresponding log-transformed TEC and AREE by Z_1 and Z_2. Corresponding log-biomarker values, say W_1 and W_2, are assumed to adhere to a classical measurement model so that

$$W_1 = Z_1 + E_1 \quad \text{and} \quad W_2 = Z_2 + E_2,$$

where the (mean 0) error terms E_1 and E_2 are independent of the corresponding target (Z_1 or Z_2) and of other study subject characteristics. In comparison, the log-transformed self-reported TEC and AREE, denoted by Q_1 and Q_2, respectively, are allowed to have a more flexible measurement model,

$$Q_1 = a_0 + a_1 Z_1 + a_2 Z_2 + a_3 Q_3 + a_4^t V + e_1 \quad \text{and}$$
$$Q_2 = b_0 + b_1 Z_1 + b_2 Z_2 + b_3 Q_3 + b_4^t V + e_2,$$

where the a's and b's are constants, V is a vector (superscript t denotes vector transpose) of study subject characteristics that includes all other modeled variables in the disease risk model, $Q_3 = $ BMI has been separated from other study subject characteristics, and the "noise" terms (e_1, e_2) are independent of (Z_1, Z_2) given (V, Q_3). These exposure measures, Q_1 and Q_2, aim to assess short-term energy and activity levels, whereas BMI can be viewed as reflecting energy consumption and activity levels, as well as energy balance specifically, over the lengthy period of time relevant to the targets Z_1 and Z_2. Hence, we regard Q_3 as an additional source of information on TEC and AREE, and we specify the following model of the same form for BMI:

$$Q_3 = c_0 + c_1 Z_1 + c_2 Z_2 + c_3^t V + e_3.$$

A joint normality assumption for (Z_1, Z_2, Q_1, Q_2, Q_3) given V then gives the expectation of (Z_1, Z_2) given (Q_1, Q_2, Q_3, V) as a linear function of these variables. Under our biomarker modeling assumption, which includes independence of (E_1, E_2) from (e_1, e_2, e_3) given V, this expectation can be estimated by linear regression of W_1 and W_2 on (Q_1, Q_2, Q_3, V), as we do to develop calibration equations for Z_1 and Z_2. Note that it will be unnecessary to include BMI separately in the disease risk model under the rather strong assumption that its relationship with disease is fully "captured" by its role as a source of information on long-term TEC and AREE. We exclude BMI from the risk model in analyses of calibrated TEC and AREE presented here.

Additional analyses were conducted separately for women whose BMI values were less than 25 (normal weight or underweight) and for those whose BMI values were 25 or more (overweight or obese) at enrollment. Updated regression calibration TEC and AREE estimates were developed separately in the 2 baseline BMI groups as described above for use in these analyses. Women provided written informed consent for their WHI participation, and protocols were approved by the institutional review boards at the Fred Hutchinson Cancer Research Center (Seattle, Washington) and each participating clinical center.

RESULTS

Table 1 shows the baseline (at WHIOS enrollment) characteristics of women in the WHIOS and the NPAAS, including frequency information on all variables used in regression modeling. Geometric means and 95% confidence intervals for both self-reported and calibrated TEC and AREE are also shown with estimates from simple calibration equations that include only log-transformed self-reported TEC, log-transformed self-reported AREE, BMI, age, race, and family income. Biomarker-corrected TEC and AREE values are considerably larger than corresponding self-reported values. Table 2 shows incidence rates and numbers of women experiencing disease events during the observational study follow-up periods, following the exclusions described in the Methods.

TEC and AREE estimates were simultaneously related to disease outcomes using Cox regression with and without calibration of TEC and AREE in Tables 3–5. For convenience of

Table 2. Incidence Rates Per 1,000 Person-Years and Numbers of Events From the Women's Health Initiative Observational Study for Cardiovascular Diseases and Cancers (From Baseline Through September 30, 2010) and for Diabetes (From Baseline Through September 17, 2012)

Disease	No. of Cases	No. of Women	Incidence
Cancer			
Bladder	228	68,712	0.30
Breast	3,798	65,347	5.33
Colon	677	64,055	0.94
Endometrial	584	68,298	0.76
Kidney	182	68,298	0.24
Leukemia	237	68,712	0.31
Lung	859	68,712	1.12
Lymphoma	458	68,712	0.60
Obesity-related[a]	5,440	68,224	7.40
Ovarian	348	65,347	0.47
Pancreatic	220	68,712	0.29
Rectal	103	65,384	0.14
Total invasive cancer	9,227	68,224	12.78
Cardiovascular disease			
CABG and PCI	1,968	56,390	3.12
Coronary death	550	56,390	0.86
Heart failure	780	56,390	1.22
MI (nonfatal)	1,397	56,390	2.20
Stroke			
Hemorrhagic	233	56,390	0.36
Ischemic	1,136	56,390	1.78
Total stroke	1,462	56,390	2.30
Total CHD (MI and coronary death)	1,660	56,390	2.61
Total CVD (CHD and stroke)	2,967	56,390	4.70
Total CVD (including CABG and PCI)	4,212	56,390	6.75
Diabetes mellitus	6,494	72,724	8.19

Abbreviations: CABG, coronary artery bypass graft; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a] Obesity-related cancer includes breast, colon, rectal, endometrial, and kidney cancers.

interpretation, hazard ratios for 20% increases in TEC and AREE are presented. Calibration equation coefficients for log-TEC and log-AREE for each clinical outcome are given in Web Table 2.

Table 3 documents strong positive associations of calibrated TEC and inverse associations of calibrated AREE with risks of coronary disease and ischemic stroke. Hazard ratios for a 20% increase in TEC were approximately 1.5 for most coronary disease outcomes, whereas corresponding hazard ratios for a 20% increase in AREE were approximately 0.8. Hazard ratios were particularly extreme for the risks of

coronary death and congestive heart failure. Similar hazard ratios were observed for ischemic stroke, whereas hazard ratio patterns were quite different, though nonsignificant, for hemorrhagic stroke. In contrast, uncalibrated TEC and AREE associations with CVD incidence were weak or nonexistent.

Total and site-specific cancer findings (Table 4) were similar to those for CVD. Positive associations with calibrated TEC and inverse associations with calibrated AREE were found for total invasive cancers, obesity-related cancer, breast cancer, and rectal cancer. Additionally, TEC hazard ratios were elevated for colon cancer, endometrial cancer, and kidney cancer, even though corresponding AREE hazard ratios were not significant; the pancreatic cancer hazard ratio was lower at higher AREE, even though the TEC hazard ratio was not significant. A 20% increase in calibrated TEC was associated with a hazard ratio of approximately 1.7 for obesity-related cancers, with a corresponding hazard ratio of approximately 0.8 for a 20% increase in AREE. Corresponding estimated hazard ratios were essentially null without measurement error correction.

Analyses of calibrated TEC and AREE in relation to diabetes incidence, as shown in Table 5, yielded a strong positive association with calibrated TEC and a strong inverse association with calibrated AREE. The estimated associations were comparatively much weaker without measurement error correction.

Table 6 shows analyses of the same type as those shown in Tables 3–5 separately for women with BMI values of less than 25 (normal weight or underweight) and those with BMI values of 25 or more (overweight or obese) at baseline. Because the number of cases is rather small for some outcomes in the normal-weight/underweight stratum, and the confidence intervals are correspondingly wide, hazard ratios are presented for only the composite outcomes. Hazard ratio estimates are above 1 for TEC and below 1 for AREE for each disease category shown, and they are far from significantly different between the 2 BMI groups (all P values > 0.50 for both TEC and AREE for between–BMI strata hazard ratio comparisons). Note, however, that hazard ratios in the normal-weight/underweight stratum tended to be somewhat closer to the null, and some corresponding confidence intervals included unity.

DISCUSSION

The analyses presented here suggest important positive associations for TEC and important inverse associations for AREE with the risk of CVDs, cancers, and diabetes in postmenopausal women. For example, a 20% reduction in TEC corresponds to an approximately one-third lower incidence of CVDs and invasive cancers and an approximately three-fourths lower diabetes incidence; a 20% increase in AREE corresponds to an approximately one-fourth lower incidence of CVDs and invasive cancers and an approximately two-thirds lower diabetes incidence. Simultaneous TEC and AREE changes of these magnitudes are associated with an approximately 50% lower risk of major CVDs and cancers and an approximately 7-fold lower diabetes incidence. If confirmed by further research, such estimates would place TEC and AREE in the category of major causes of avoidable

Table 3.   Estimated Hazard Ratios for 20% Increases in Total Energy Consumption and Activity-Related Energy Expenditure With and Without Calibration to Correct for Measurement Error, for Various Cardiovascular Disease Categories in the Women's Health Initiative Observational Study From Baseline (in 1994–1998) Through September 30, 2010

Disease Category	Uncalibrated				Calibrated			
	TEC		AREE		TEC		AREE	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
CABG and PCI	1.01	0.99, 1.03	1.01	0.99, 1.03	1.43	1.19, 1.70	0.90	0.79, 1.03
Congestive heart failure	1.04	1.01, 1.08	0.97	0.95, 1.00	3.51	2.12, 5.82	0.57	0.41, 0.79
Coronary death	0.97	0.94, 1.02	0.97	0.94, 1.00	2.22	1.36, 3.61	0.63	0.46, 0.86
Myocardial infarction (nonfatal)	1.00	0.98, 1.03	0.99	0.97, 1.01	1.49	1.13, 1.97	0.80	0.67, 0.97
Stroke								
Hemorrhagic	0.94	0.88, 0.99	1.03	0.99, 1.08	0.47	0.21, 1.07	1.37	0.85, 2.20
Ischemic	0.98	0.96, 1.01	0.99	0.97, 1.01	1.55	1.14, 2.10	0.78	0.64, 0.94
Total	0.97	0.95, 1.00	0.99	0.98, 1.01	1.36	1.05, 1.76	0.83	0.69, 0.99
Total CHD (MI and coronary death)	1.00	0.98, 1.02	0.99	0.97, 1.01	1.57	1.19, 2.06	0.78	0.65, 0.95
Total CVD (CHD and stroke)	0.99	0.97, 1.00	0.99	0.98, 1.00	1.49	1.18, 1.88	0.80	0.69, 0.92
Total CVD (including CABG and PCI)	1.00	0.99, 1.01	1.00	0.99, 1.01	1.49	1.23, 1.81	0.83	0.73, 0.93

Abbreviations: AREE, activity-related energy expenditure; CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; TEC, total energy consumption.

disease, as was long since heralded by Doll and Peto (30) for cancer death. Furthermore, analyses that stratify on BMI suggest that positive TEC and inverse AREE associations with chronic disease risk may extend to women of normal weight, though there were few women in the WHIOS with baseline BMI values near or below the low end of the normal-weight range.

The analyses presented here rely on modeling assumptions that may be controversial. Chief among these is the specific role of BMI. Our assumption is that variations in BMI arise substantially from variations in energy consumption and physical activity patterns over time, so that BMI provides a source of information, in addition to

Table 4.   Estimated Hazard Ratios for 20% Increases in Total Energy Consumption and Activity-Related Energy Expenditure, With and Without Calibration to Correct for Measurement Error, for Various Cancer Categories in the Women's Health Initiative Observational Study From Baseline (in 1994–1998) Through September 30, 2010

Cancer Category	Uncalibrated				Calibrated			
	TEC		AREE		TEC		AREE	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Bladder	1.03	0.97, 1.10	0.96	0.92, 1.00	1.80	0.88, 3.69	0.68	0.42, 1.09
Breast	1.01	0.99, 1.02	1.00	0.99, 1.01	1.47	1.18, 1.84	0.82	0.71, 0.96
Colon	1.00	0.96, 1.03	1.00	0.97, 1.03	1.86	1.18, 2.93	0.83	0.66, 1.04
Endometrial	1.08	1.04, 1.12	1.01	0.98, 1.05	2.72	1.44, 5.13	0.77	0.49, 1.21
Kidney	1.05	0.98, 1.12	1.02	0.96, 1.07	2.94	1.37, 6.28	0.62	0.35, 1.12
Leukemia	1.01	0.95, 1.07	0.98	0.93, 1.02	1.48	0.70, 3.12	0.74	0.47, 1.18
Lung	0.99	0.96, 1.01	0.97	0.95, 1.00	1.14	0.74, 1.76	0.79	0.60, 1.03
Lymphoma	1.08	1.03, 1.13	1.00	0.96, 1.03	0.99	0.48, 2.07	1.16	0.69, 1.94
Obesity-related[a]	1.02	1.00, 1.03	1.00	0.99, 1.01	1.71	1.33, 2.21	0.79	0.65, 0.94
Ovarian	1.00	0.95, 1.05	1.01	0.98, 1.05	0.85	0.43, 1.68	1.12	0.73, 1.71
Pancreatic	0.95	0.89, 1.01	0.97	0.92, 1.01	2.06	0.98, 4.33	0.61	0.37, 1.00
Rectal	1.01	0.92, 1.10	0.99	0.93, 1.05	2.75	1.10, 6.83	0.51	0.27, 0.99
Total invasive	1.01	1.00, 1.02	0.99	0.99, 1.00	1.43	1.17, 1.73	0.84	0.73, 0.96

Abbreviations: AREE, activity-related energy expenditure; CI, confidence interval; HR, hazard ratio; TEC, total energy consumption.
[a] Obesity-related cancer includes breast, colon, rectal, endometrial, and kidney cancers.

Table 5. Estimated Hazard Ratios for 20% Increases in Total Energy Consumption and Activity-Related Energy Expenditure, With and Without Calibration to Correct for Measurement Error, for Diabetes Incidence in the Women's Health Initiative Observational Study, From Baseline (in 1994–1998) Through September 17, 2012

Outcome Category	Uncalibrated				Calibrated			
	TEC		AREE		TEC		AREE	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Diabetes mellitus	1.06	1.04, 1.07	1.01	1.00, 1.02	4.17	2.68, 6.49	0.60	0.44, 0.83

Abbreviations: AREE, activity-related energy expenditure; CI, confidence level; HR, hazard ratio; TEC, total energy consumption.

self-reported energy and activity, on TEC and AREE. In fact, BMI provides exposure information that reflects the long-term exposures that are likely to be of greatest interest in epidemiologic research. In comparison, the corresponding self-reported data target comparatively short-term diet and physical activity patterns.

An important aspect of our assumptions is that BMI is assumed to be unrelated to disease risk independently of diet and physical activity; that is, BMI is assumed not to be a confounder of these associations, conditional on long-term TEC and AREE history and on other modeled confounding factors. This seems to be a sensible assumption, but not one that can be fully tested with available data.

In contrast, the inclusion of BMI data in the disease risk model would yield analyses that essentially examine disease associations with short-term TEC and AREE data conditional on long-term energy balance information. In fact, most of the hazard ratio estimates in Tables 3–5 became quite unstable (data not shown) when BMI was added to the disease risk model, presumably attesting to the limited incremental signal from the self-reported TEC and AREE data beyond that reflected in BMI.

An alternate analysis of these data would include BMI in the disease risk model and would induce a disease rate model as a function of TEC and AREE by averaging over BMI to estimate marginal TEC and AREE associations with disease risk (31, 32). Although this approach involves fewer assumptions, the hazard ratio estimates that arise would seem to address associations of lesser public health relevance, and results can be expected to be sensitive to the magnitude of measurement error correlations among repeat biomarker values on individual study subjects.

Also, some readers may question our classical measurement model assumptions for TEC and AREE biomarkers, given our focus on long-term TEC and AREE. For example, population changes with aging are well known for both TEC and AREE, and the biomarker data are collected toward the end of the long-term exposure period targeted. However, our biomarker model could be relaxed to include a nonnull measurement error mean without any change in the analyses in Tables 3–6. In fact, because the Cox models we applied stratified on age at baseline in 5-year periods, this nonnull mean could vary by age category without affecting these analyses.

Biomarker assessments, in conjunction with self-reported assessments across years of cohort follow-up would allow valuable refinements of the analyses presented here. If the period of such data collection is long enough, one could explore the association of BMI with disease, given corresponding biomarker and self-reported histories, and could relax the corresponding independence assumption as necessary.

The uncalibrated TEC and AREE self-reported assessments show few relationships with risk for the diseases considered here, presumably because of the substantial random and systematic biases that attend these assessments (12, 13, 17), and because they target exposure over a short time period.

Table 6. Estimated Hazard Ratios for 20% Increases in Calibrated Total Energy Consumption and Calibrated Activity-Related Energy Expenditure for Cardiovascular Diseases, Cancers, and Diabetes According to BMI[a] at Baseline (in 1994–1998) Through 2010 (for Cancer, CHD, and CVD) or 2012 (for Diabetes) in the Women's Health Initiative Observational Study

Disease Category	Women With BMI < 25				Women With BMI ≥ 25			
	TEC		AREE		TEC		AREE	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Diabetes mellitus	2.74	0.98, 7.68	0.75	0.44, 1.28	3.58	1.84, 6.96	0.65	0.48, 0.87
Obesity-related cancer[b]	1.77	1.10, 2.84	0.80	0.62, 1.02	1.66	1.26, 2.20	0.80	0.66, 0.97
Total CHD (MI and coronary death)	1.47	0.77, 2.79	0.83	0.56, 1.23	1.80	1.19, 2.71	0.76	0.61, 0.95
Total CVD (including CABG and PCI)	1.16	0.63, 2.15	0.91	0.65, 1.27	1.34	1.03, 1.74	0.87	0.75, 1.00
Total invasive cancer	1.42	1.05, 1.94	0.88	0.76, 1.01	1.52	1.10, 2.09	0.81	0.66, 0.99

Abbreviations: AREE, activity-related energy expenditure; BMI, body mass index; CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence level; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention; TEC, total energy consumption.

[a] Weight (kg)/height (m)^2.

[b] Obesity-related cancer includes breast, colon, rectal, endometrial, and kidney cancers.

The associations of self-reported TEC and AREE with the corresponding biomarker assessments considered here are weak, as was the case for other dietary and activity assessment procedures studied in the NPAAS (13, 14, 17), supporting the need for continued research toward improved diet and physical activity assessment methods.

In summary, the calibrated TEC and AREE analyses presented here imply that further efforts are needed to definitively evaluate their associations with the risk of major chronic diseases in populations of interest. Longitudinal data over a substantial period of cohort follow-up, using both biomarkers and strong self-reported assessments, could do much to strengthen the related research agenda. Meanwhile, the provocative analyses summarized here suggest that these fundamental exposures may be major drivers of many of the chronic diseases that are so prominent in Western societies, at least among postmenopausal women.

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REFERENCES

1. Parkin DM, Whelan SR, Ferlay J, et al. *Cancer Incidence in Five Continents*. Lyon, France: International Agency for Research on Cancer; 1998. (IARC Scientific Publication No. 143).
2. Ziegler RG, Hoover RN, Pike MC, et al. Migration patterns and breast cancer risk in Asian-American women. *J Natl Cancer Inst*. 1993;85(22):1819–1827.
3. World Health Organization. *Diet, Nutrition and the Prevention of Chronic Diseases: Report of a Joint WHO/FAO Expert Consultation*. Geneva, Switzerland: World Health Organization; 2003:88. (WHO Technical Report Series, No. 916).
4. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. Washington, DC: American Institute for Cancer Research; 2007.
5. Prentice RL, Huang Y, Kuller LH, et al. Biomarker-calibrated energy and protein consumption and cardiovascular disease risk among postmenopausal women. *Epidemiology*. 2011;22(2): 170–179.
6. Prentice RL, Shaw PA, Bingham SA, et al. Biomarker-calibrated energy and protein consumption and increased cancer risk among postmenopausal women. *Am J Epidemiol*. 2009;169(8):977–989.
7. Tinker LF, Sarto GE, Howard BV, et al. Biomarker-calibrated dietary energy and protein intake associations with diabetes risk among postmenopausal women from the Women's Health Initiative. *Am J Clin Nutr*. 2011;94(6): 1600–1606.
8. Beasley JM, LaCroix AZ, Neuhouser ML, et al. Protein intake and incident frailty in the Women's Health Initiative Observational Study. *J Am Geriatr Soc*. 2010;58(6): 1063–1071.
9. Beasley JM, Aragaki AK, LaCroix AZ, et al. Higher biomarker-calibrated protein intake is not associated with impaired renal function in postmenopausal women. *J Nutr*. 2011;141(8): 1502–1507.
10. Prentice RL, Pettinger M, Tinker LF, et al. Regression calibration in nutritional epidemiology: example of fat density and total energy in relationship to postmenopausal breast cancer. *Am J Epidemiol*. 2013;178(11):1663–1672.
11. Prentice RL, Neuhouser ML, Tinker LF, et al. An exploratory study of respiratory calibration and association with postmenopausal breast cancer. *Cancer Epidemiol Biomarker Prev*. 2013;22(12):2374–2383.
12. Neuhouser ML, Tinker L, Shaw PA, et al. Use of recovery biomarkers to calibrate nutrient consumption self-reports in the Women's Health Initiative. *Am J Epidemiol*. 2008;167(10): 1247–1259.
13. Prentice RL, Mossavar-Rahmani Y, Huang Y, et al. Evaluation and comparison of food records, recalls, and frequencies for energy and protein assessment by using recovery biomarkers. *Am J Epidemiol*. 2011;174(5):591–603.

14. Prentice RL. Covariate measurement errors and parameter estimation in a failure time regression model. *Biometrika*. 1982; 69(2):331–342.
15. Wang CY, Hsu L, Feng ZD, et al. Regression calibration in failure time regression. *Biometrics*. 1997;53(1):131–145.
16. Carroll RJ, Ruppert D, Stefanski LA, et al. *Measurement Error in Nonlinear Models: a Modern Perspective*. 2nd ed. Boca Raton, FL: Chapman and Hall/CRC; 2006.
17. Neuhouser ML, Di C, Tinker LF, et al. Physical activity assessment: biomarkers and self-report of activity-related energy expenditure in the WHI. *Am J Epidemiol*. 2013;177(6): 576–585.
18. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition and the Prevention of Cancer: a Global Perspective*. Washington, DC: American Institute for Cancer Research; 1997, p. 371.
19. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19(1):61–109.
20. Hays J, Hunt JR, Hubbell FA, et al. The Women's Health Initiative recruitment methods and results. *Ann Epidemiol*. 2003;13(9 suppl):S18–S77.
21. Langer RD, White E, Lewis CE, et al. The Women's Health Initiative observational study: baseline characteristics of participants and reliability of baseline measures. *Ann Epidemiol*. 2003;13(9 suppl):S107–S121.
22. Patterson RE, Kristal AR, Tinker LF, et al. Measurement characteristics of the Women's Health Initiative food frequency questionnaire. *Ann Epidemiol*. 1999;9(3):178–187.
23. Johnson-Kozlow M, Rock CL, Gilpin EA, et al. Validation of the WHI brief physical activity questionnaire among women diagnosed with breast cancer. *Am J Health Behav*. 2007;31(2): 193–202.
24. Ainsworth BE, Haskell WL, Whitt MC. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000;32(9 suppl): S498–S504.
25. Schoeller DA, Hnilicka JM. Reliability of the doubly labeled water method for the measurement of total daily energy expenditure in free-living subjects. *J Nutr*. 1996;126(1): 348S–354S.
26. Horner NK, Lampe JW, Patterson RE, et al. Indirect calorimetry protocol development for measuring resting metabolic rate as a component of total energy expenditure in free-living postmenopausal women. *J Nutr*. 2001;131(8): 2215–2218.
27. Curb JD, McTiernan A, Heckbert SR, et al. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol*. 2003;13(9 suppl):S122–S128.
28. Margolis KL, Qi L, Brzyski R, et al. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. *Clin Trials*. 2008;5(3):240–247.
29. Cox DR. Regression analysis and life tables (with discussion). *J R Stat Soc B*. 1972;34(2):187–220.
30. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst*. 1981;66(6):1191–1308.
31. Freedman LS, Midthune D, Carroll RJ, et al. Using regression calibration equations that combine self-reported intake and biomarker measures to obtain unbiased estimates and more powerful tests of dietary associations. *Am J Epidemiol*. 2011; 174(11):1238–1245.
32. Prentice RL, Huang Y. Measurement error modeling and nutritional epidemiology association analyses. *Can J Stat*. 2011;39(3):498–509.