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Available at: https://works.bepress.com/di/27/
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Initially submitted March 13, 2014; accepted for publication May 20, 2014.

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 (WHO) 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 WHO 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 WHO 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
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
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,

$$ Q_1 = a_0 + a_1Z_1 + a_2Z_2 + a_3Q_3 + a'_1V + e_1 \quad \text{and} \quad Q_2 = b_0 + b_1Z_1 + b_2Z_2 + b_3Q_3 + b'_1V + e_2, $$

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:

$$ Q_3 = c_0 + c_1Z_1 + c_2Z_2 + c'_1V + e_3. $$

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
interpretation, hazard ratios for 20% increases in TEC and AREE are presented. Calibration error correction. 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 they are far from significant differences 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 risk.
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

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.

### 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

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

**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.

### 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

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

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

* Obesity-related cancer includes breast, colon, rectal, endometrial, and kidney cancers.

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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 correspond-
ing self-reported data target comparatively short-term diet
and physical activity patterns.

An important aspect of our assumptions is that BMI is as-
sumed 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 haz-
ard 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 assump-
tions, the hazard ratio estimates that arise would seem to
address associations of lesser public health relevance, and re-
sults can be expected to be sensitive to the magnitude of mea-
surement error correlations among repeat biomarker values
on individual study subjects.

Also, some readers may question our classical measure-
ment model assumptions for TEC and AREE biomarkers,
given our focus on long-term TEC and AREE. For example,
the Cox models we applied stratified on age at baseline in
5-year periods, this nonnull mean

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

<table>
<thead>
<tr>
<th>Outcome Category</th>
<th>Unadjusted</th>
<th>Calibrated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEC</td>
<td>AREE</td>
</tr>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.06</td>
<td>1.04, 1.07</td>
</tr>
<tr>
<td></td>
<td>4.17</td>
<td>2.68, 6.49</td>
</tr>
</tbody>
</table>

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

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 BMIa at Baseline (in 1994–1998) Through 2010 (for Cancer, CHD, and CVD) or
2012 (for Diabetes) in the Women’s Health Initiative Observational Study

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Women With BMI &lt; 25</th>
<th>Women With BMI ≥ 25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEC 95% CI</td>
<td>AREE 95% CI</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.74 0.98, 7.68</td>
<td>0.75 0.44, 1.28</td>
</tr>
<tr>
<td>Obesity-related cancerb</td>
<td>1.77 1.10, 2.84</td>
<td>0.80 0.62, 1.02</td>
</tr>
<tr>
<td>Total CHD (MI and coronary death)</td>
<td>1.47 0.77, 2.79</td>
<td>0.83 0.56, 1.23</td>
</tr>
<tr>
<td>Total CVD (including CABG and PCI)</td>
<td>1.16 0.63, 2.15</td>
<td>0.91 0.65, 1.27</td>
</tr>
<tr>
<td>Total invasive cancer</td>
<td>1.42 1.05, 1.94</td>
<td>0.88 0.76, 1.01</td>
</tr>
</tbody>
</table>

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.

ACKNOWLEDGMENTS

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This work was supported by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services (contracts HHSN 268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C), and National Cancer Institute (grants R01 CA119171 and P01 CA53996).

We thank the following investigators in the Women’s Health Initiative program: Jacques E. Rossouw, Shari Ludlam, Dale Burwen, Joan McGowan, Leslie Ford, and Nancy Geller in the program office; Garnet L. Anderson and Charles L. Kooperberg in the clinical coordinating center; and Barbara V. Howard, Marcia L. Stefanick, Rebecca Jackson, Jean Wactawski-Wende, Marian C. Limacher, Robert M. Wallace, Lewis H. Kuller, and Sally A. Shumaker at research and academic centers.

Decisions concerning study design, data collection and analysis, interpretation of the results, preparation of the manuscript, and the decision to submit the manuscript for publication resided with committees comprising Women’s Health Initiative investigators that included representatives of the National Heart, Lung, and Blood Institute. The contents of the paper are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Conflict of interest: none declared.

REFERENCES


