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How Much Should We Eat? The Association Between Energy Intake and Mortality in a 36-Year Follow-Up Study of Japanese-American Men

Bradley J. Willcox,[1,2,3] Katsuhiko Yano,[1,2] Randi Chen,[1] D. Craig Willcox,[4] Beatriz L. Rodriguez,[1,2,3] Kamal H. Masaki,[1,2,3] Timothy Donlon,[5] Brandi Tanaka,[1,2] and J. David Curb[1,2,3]

[1]Pacific Health Research Institute, Honolulu, Hawaii.
[2]Honolulu Heart Program, Kuakini Medical Center, Hawaii.
[3]Department of Geriatric Medicine and Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu.
[4]College of Nursing, Okinawa Prefectural University, Japan.
[5]Cancer Research Center of Hawaii, University of Hawaii, Honolulu.

Energy restriction extends life span and lowers mortality from age-related diseases in many species, but the effects in humans are unknown. We prospectively examined this relationship in a large epidemiological study of Japanese-American men. We followed 1915 healthy nonsmokers, aged 45–68 years at study onset, for 36 years. Twenty-four-hour recall of diet was recorded at baseline, and follow-up was for all-cause mortality. After adjustment for age and other confounders, there was a trend toward lower mortality in the second quintile of energy intake, suggesting that men who consumed 15% below the group mean were at the lowest risk for all-cause mortality. Increased mortality was seen with intakes below 50% of group mean. Thus, we observed trends between low energy intake and reduced risk for all-cause mortality in humans until energy intake fell to less than half the group mean, consistent with previous findings in other species.

MCKAY, in the 1930s, was the first to report the remarkable observation that energy restriction, usually referred to as caloric restriction (CR), is a consistent and reproducible method for prolonging life span and decreasing risk for numerous age-associated diseases in rodents (1). This observation has since been reproduced experimentally across numerous species, and preliminary evidence from experiments in progress with nonhuman primates suggests that these observations may hold for them as well (2).

The mechanism for increased life span remains elusive. There have been many proposed mechanisms including less oxidative and glucose-induced damage to tissues and genetic material, reduced insulin signaling, and hormesis (3,4). Hormesis is a beneficial action resulting from the response of an organism to a low-intensity stressor such as the higher levels of glucocorticoids seen in energy-restricted rodents with longer life spans (5). Wide-ranging changes in gene expression have been observed in energy-restricted animals, suggesting that multiple mechanisms may come into play (6,7).

That CR may be a factor in human longevity is more difficult to ascertain since the human life span makes such investigations impractical (8). Shorter-term studies are currently under way with human volunteers, but do not have mortality as an end-point (8,9). Epidemiological evidence from long-lived human populations is sparse but has been used to support the CR hypothesis (8,10). For example, the Japanese have low energy consumption relative to Caucasians and have the greatest life expectancy of all countries (11). The Okinawan Japanese, in particular, have the lowest energy consumption among the Japanese and have the longest life expectancy, highest prevalence of centenarians, and lowest mortality from CR-linked diseases such as diabetes, cardiovascular disease, and certain cancers (11,12).

These cross-sectional data are open to multiple interpretations and sources of bias. Few longitudinal studies exist on humans that have collected accurate and reliable information on energy intake, and confounding often exists between energy intake, other nutritional factors, smoking, physical activity, and other diseases, the effects of which are often difficult to separate. Furthermore, nutritional habits often change over time, so measurement of energy intake at study onset may not reflect life-long energy intake. Finally, follow-up is usually not long enough to address longevity as an outcome.

The Honolulu Heart Program (HHP) has among the longest follow-up of any cohort study. With 36 years of follow-up, it is a large and fairly homogeneous cohort of Japanese-American men with a very long life expectancy. Therefore, it is one of the few studies that can prospectively examine the relationship between energy intake and mortality in humans. We address two questions: 1) What is the relationship between energy intake and mortality across a broad spectrum of energy intake in apparently healthy, nonsmoking men? 2) At what point does low energy intake become associated with increased mortality?

Methods

Study Population and Procedures

The HHP is a prospective study of cardiovascular disease among 8006 Japanese-American men who were born between 1900 and 1919 and lived on the island of Oahu, Hawaii, in 1965. The cohort recruitment and study design and procedures have been described elsewhere (13,14). At the time of study enrollment (1965–1968), participants were aged 45 to 68 years.

At the baseline exam, information was collected on sociodemographic characteristics, medical history, anthropometric measures, smoking status, alcohol consumption, physical activity, and blood chemistry. Blood pressure was measured three times in the sitting position using a sphygmomanometer. A 12-lead resting electrocardiogram was recorded. Body weight was measured with the participants in light clothing and without shoes. Body mass index (BMI; the weight in kilograms divided by the square of the height in meters) was calculated. A physical activity index (PAI) was calculated as a weighted sum of the number of hours per day participants spent at each of five levels of activity based on questionnaires similar to those used in the Framingham Study (15). Dietary assessment was performed at baseline by a dietitian using the 24-hour recall method. At the second exam, 2 years later, validation and reliability of diet intake was studied on a random subsample (329 men) using both the 24-hour recall method and 7-day food records (16). Alcohol intake, expressed as ounces of ethanol per month, was estimated on the basis of each participant's usual consumption of beer, wine, and liquor using conversion rates determined by the *USDA Handbook #8* (17). Occupations were coded using the 1970 U.S. Census Alphabetical Listings for Industries and Occupations (18).

Since the onset of the HHP in 1965, information on the development of incident coronary heart disease (CHD) and stroke as well as mortality from all causes have been obtained through monitoring, obituaries in local newspapers (English and Japanese), and surveillance of hospital discharges. Also, state health department records of death certificates have been analyzed through the end of 2001. For each death, an underlying cause was assigned by a medical review panel on the basis of relevant clinical and autopsy records and coded according to the *International Classification of Diseases, Eighth Revision* (ICD-8) (19). A follow-up survey in the 1991–1993 exam found that only 5 men could not be traced for mortality information (20).

Statistical Analysis

In the present analysis, all men with a history of CHD, stroke, cancer, or diabetes and those who died within 2 years of follow-up were excluded in order to eliminate possible biases that might be caused by apparent or latent preexisting diseases. This analysis was also repeated with early deaths included (21). Also, we excluded current and past smokers from analysis. The presence of these conditions could affect both energy intake and subsequent mortality. Furthermore, all men who reported atypical diet were excluded.

We investigated whether energy intake was related to mortality using the remaining 1915 men. These men were classified into quintiles of daily energy intake. Crude and age-adjusted rates of all-cause mortality per 1000 person-years were estimated according to the quintile of energy intake based on the 36 years of follow-up information. Age adjustment was done by the direct method using the age distribution of the 1915 men who were apparently healthy and never smoked at the baseline exam. Age-adjusted mortality rates across the quintiles of energy intake were derived based on the analysis of covariance methods (22). Similar analysis was used to test for trends in a risk factor across the quintiles of energy intake after adjusting for age.

To estimate the independent effect of energy intake (as both continuous and categorical variables) on the risk of mortality, the Cox proportional hazards model was used. (23) We considered three models for the analysis. Model 1 included only age as a covariate. Model 2 additionally included BMI, PAI, and usual alcohol consumption. Model 3 included intakes of major nutrients (g/day) along with total energy intake. The middle quintile group was chosen as the reference group (i.e., risk = 1). Then, in order to investigate the effect of low energy intake in more detail, the lower half of the study cohort was further divided based on the extent of reduced energy intake by 10% intervals beginning 11% below the overall group mean. The reference group consisted of men with energy intake ± 10% of the overall mean. Thus, there were five subgroups of below-average (CR) energy intake by percentage of the group mean: –11 to –20, –21 to –30, –31 to –40, –41 to –50, and –51 or less, with the numbers of men in each group equaling 238, 208, 151, 91, and 41, respectively. The age-adjusted relative risk of mortality was obtained for each of these groups using the middle group as a reference.

A ''U''-shaped relationship between energy intake and mortality was also assessed in a separate model using quadratic terms of energy intake. All reported p values were based on two-sided tests of significance (except for the evaluation of the point at which very low energy intake would become associated with increased mortality, in which one-sided p values were employed). A p value of .05 was considered statistically significant.

Results

Correlates of Energy Intake

Nonsmoking, apparently healthy men with lower energy intake at baseline tended to be older, heavier (except the lowest group), consume less alcohol, were less physically active, and ate a higher percentage of their diet as protein and carbohydrates, and less as fat compared with those who had higher caloric intake. There were no significant differences in terms of BMI (Table 1).

Mortality Risk by Quintile of Energy Intake

Risk of mortality after adjustment for age, and other potential confounders including alcohol consumption, physical activity, and macronutrient composition was not significantly different across a wide range of energy intake, from a low of 512 to a high of 6480 kcal energy per day, in

Table 1. Characteristics of the Study Population by Quintile of Energy Intake

Variables	Total Energy Intake Per Day* (Quintiles) Q1	Q2	Q3	Q4	Q5	*P* (Trend)†
Calories (mean)	1407	1882	2214	2581	3212	
Calories (range)	512–1701	1705–2061	2065–2366	2368–2806	2807–6480	
Number of participants	383	383	384	382	383	
(deaths)	(243)	(229)	(221)	(233)	(210)	
Age	56.6	55.1	54.6	53.8	53.2	<.0001
Alcohol intake (oz/mo)	5.6	6.2	7.4	7.5	12.3	<.0001
Weight (kg)	64.0	62.6	63.5	63.6	65.2	.01
BMI (kg/m2)	24.6	23.9	24.2	24.0	24.3	.24
Physical Activiy Index	31.9	32.3	32.7	33.0	33.9	<.0001
% Protein	17.8	17.0	16.5	16.4	16.0	<.0001
% Fat	31.1	32.7	33.7	34.0	34.6	<.0001
% Carbohydrates	50.0	48.7	47.7	47.7	46.4	<.0001

Notes: *The percentages of energy from each nutrient do not add up to 100% because alcohol intake was counted toward total energy intake.
†Age-adjusted: all listed values are age-adjusted by analysis of covariance.
BMI = body mass index; Q = quintile.

separate analyses with linear and quadratic terms of energy intake. There was a tendency for mortality to increase from the second to fourth quintiles of energy intake ($p = .07$), suggesting that those who consumed a modestly low energy intake (an average 15% below the overall mean) have the lowest risk for all-cause mortality with progressively higher intakes associated with higher mortality (Figure 1). Caution must be exercised in the interpretation of this trend, as the ability of a single measurement of energy intake to predict long-term patterns in energy intake may be poor. Exclusion or inclusion of deaths within the first 2 years made no difference in study results since there were only 11 early deaths.

Mortality Risk by 10% Intervals of Energy Restriction

Relative risk for mortality remained stable across intervals of energy restriction until participants reported very low energy intake, equivalent to less than 50% of the reference group (± 10% of group mean energy intake; Figure 2). Energy intake of less than 50% of the reference group was associated with a 30% increased relative risk of mortality ($p = .07$).

Discussion

In this 36-year follow-up study of healthy, nonsmoking men, there were two main findings: 1) there was a trend for the age-adjusted mortality rate to be higher among men with above-average energy intake and lower among those with below-average intake; 2) mortality remained low and stable across a wide range of low energy intake until 50% of the group mean. The mortality increased only when the intake fell below 50% of the group mean energy intake.

This study is significant for several reasons. First, this is a population-based prospective study of the relationship between daily energy intake and total mortality in humans,

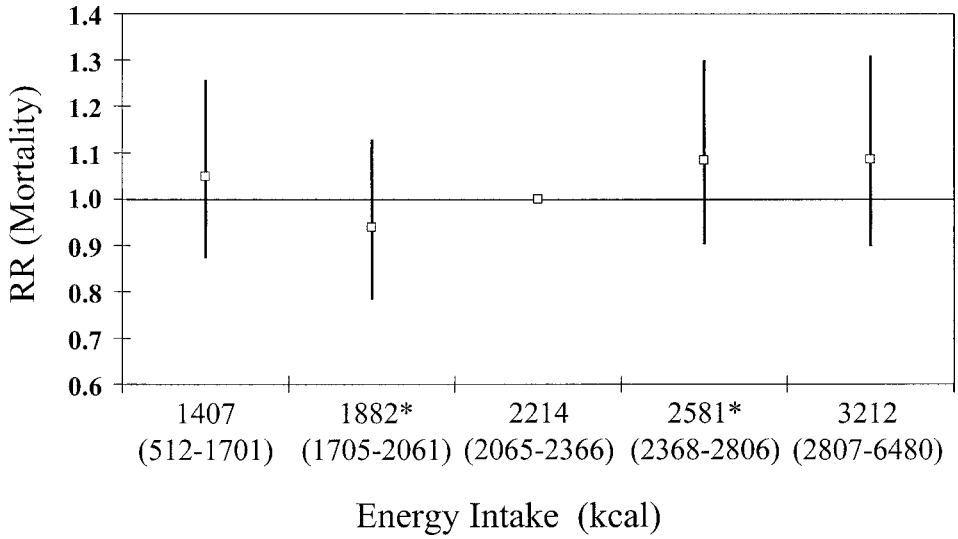

Figure 1. The relationship between mortality and energy intake. Age-adjusted relative risk for mortality by quintile of energy intake. There were no significant differences in mortality across quintiles in three separate models after adjustment for age and other confounders including alcohol, physical activity, and macronutrient composition. *Indicates trend from second to fourth quintiles of energy intake, $p = .07$. All analyses used the Cox proportional hazards model.

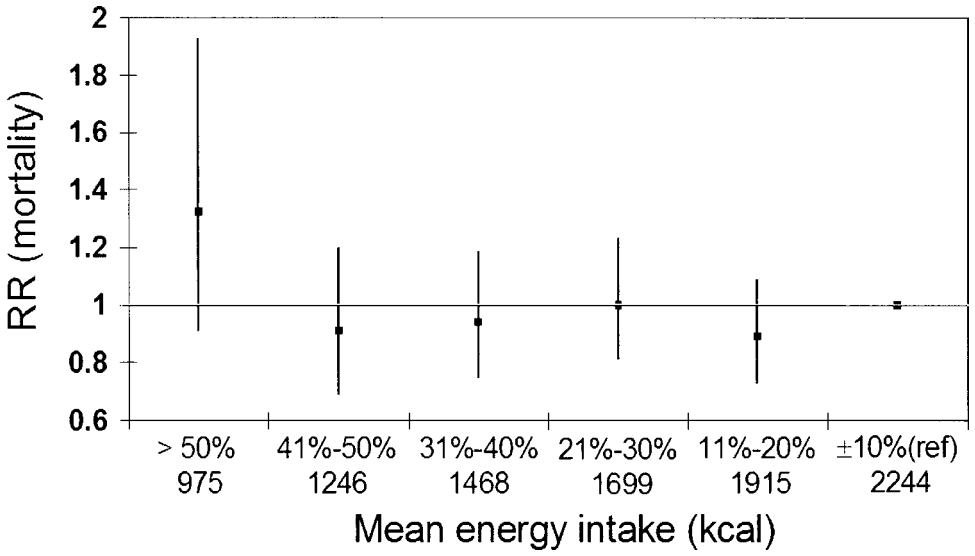

Figure 2. The age-adjusted relative risk for mortality by level of energy restriction. Less than 50% of the group mean energy intake was associated with a trend for increased mortality, $p = .07$ (Cox proportional hazards model) after adjustment for age and other risk factors (see Table 1).

and there are few such studies conducted and no studies with this long (36 years) a follow-up reported in the medical literature. Second, this study population (Japanese-American men) has among the longest life expectancy in the world for men and this study cohort has an almost complete follow-up, therefore, this is an important population for the study of factors that lead to exceptional survival. Third, despite poor quality of the measurement instrument (24-hour recall) to detect long-term relationships between diet and mortality, weak trends were still detected between energy intake and mortality, and these findings are consistent with the well-established animal literature on the mortality benefits of low caloric intake without malnutrition until approximately 50% energy restriction.

There are several strengths to this study. 1) There are well-defined study participants—nonsmoking, middle-aged Japanese-American men without chronic diseases such as CHD, stroke, cancer, and diabetes at study entry. 2) Men who reported an atypical diet were excluded from the analysis. Yet, there was a wide variation in energy intake within the study population (512–6480 kcal/day). 3) The validity of the 24-hour diet recall to estimate daily total energy intake was evaluated by the 7-day diet record obtained for a subsample (329 men) 2 years after the baseline exam. Energy intake was not significantly different by either method, and there was a reasonable ($r = .49$) correlation between reported energy intake between exams, suggesting that many study participants maintained their eating habits. 4) The study cohort was relatively thin (mean BMI = 24.2) and daily energy intake was approximately 15% lower than a similar large cohort of middle-aged Caucasian men (Framingham) measured by similar methodology (24). Therefore, the influence of obesity was smaller, and any potential role of energy intake on mortality was able to be determined more clearly. Importantly, data were available on many possible confounding variables (e.g., BMI, physical activity, alcohol consumption, macronutrients) and were entered into the multivariate model where appropriate. Such data are often not available in long-term studies of mortality.

There were several limitations to this study. First, energy intake was measured by 24-hour diet recall, without confirmatory data such as doubly-labeled water, so precise measurement of energy intake and expenditure was not possible. Inaccurate measurement due to under-reporting of food intake might have contributed to erroneous results. Typical 24-hour diet recall data underestimate energy intake by as much as 20% (25). Second, a single measurement of diet was conducted on the entire cohort during the 36-year follow-up. Therefore, there is no way to fully estimate intraindividual variability and long-term changes for all participants, which might affect the relationship between energy intake and mortality. Thus, the measurement tool was suboptimal.

Third, the true association between energy intake and mortality would likely be significantly underestimated by a single 24-hour diet recall since diets tend to change over time making it difficult to detect long-term trends (26).

Fourth, since the population included only Japanese-American men, there may be genetic or other unique features that limit the generalizability to other populations or to women. However, if such factors do exist, their identification would be critically important to the study of human longevity.

Low energy intake extends the life span in species as diverse as protozoans, fruit flies, spiders, guppies, chickens, and dogs (3). These animal studies indicate that energy intake above a certain level shortens the life span, whereas lower intake, again, to a certain level (usually up to 50%–60% ad libitum) results in a life span extension of up to 50% (1–8). In the best-studied model, laboratory rodents, energy restriction delays the onset of age-associated diseases such as cancer (particularly lymphoma, breast, and prostate cancers), diabetes, hypertension, hyperlipidemia, nephropathy, and cataracts, and virtually eliminates autoimmune disease in susceptible mouse strains (27).

Some metabolic responses to energy restriction thought to be important are lowering of blood glucose concentrations, which, in one study, showed a 20% decline after only 5 days of restricted energy intake, and lowering of plasma insulin concentrations, which can decrease by 50% after only 3 weeks (28). Concentrations of carbonyl (a marker of oxidative damage to proteins) in the brains of mice fed CR diets also appears to drop but increases within 3 to 6 weeks after the introduction of an ad libitum regimen (29).

Roth and colleagues recently reported in prospective studies of both monkeys and humans that a low body temperature, a low fasting insulin concentration, and a high blood dehydroepiandrosterone sulfate (DHEAS-S) level were associated with a longer life span (30). Previous studies of DHEA-S (31) and other age-related biomarkers from the same group of Japanese-American men in the current study support the data from Roth and colleagues.

For example, an 18-year nested case-control study of serum DHEA-S and CHD found significantly higher risk for CHD mortality in those with low baseline DHEA-S levels (31). Correlations were found at baseline between low midlife caloric intake and high serum DHEA-S levels (31). DHEA-S levels also were significantly lower in older individuals. Moreover, when compared with Caucasian men, who tend to have higher caloric intake and have significantly shorter life expectancy than this cohort, the age-related decline in DHEA-S levels appeared to be slower in the Japanese-American men. Other biomarker data linked to caloric intake, from the same cohort of Japanese-American men, also appear supportive of the caloric restriction hypothesis. For example, correlations have been found between lower blood glucose levels and lower 23-year risk for CHD mortality and all-cause mortality (32).

Recent studies employing high density oligonucleotide arrays representing thousands of aging-related genes showed that the gene expression profile in skeletal muscle (gastrocnemius) (7) and brain (cerebellum and neocortex) (33) of male C57BL/6 mice was significantly altered by CR. Specific gene expression profiles associated with the aging of individual organs so far have shown that these changes can be prevented or altered in heart, brain, and liver tissue in rodents by CR (34). These changes can occur quite rapidly and across age groups.

Since the early 1990s, studies in nonhuman primates have been under way at four different laboratories—results of which will not be known for several more years, since rhesus and squirrel monkeys, the study subjects, have life spans of up to 40 years (2). Thus far, CR-induced physiologic changes have been remarkably similar to those in rodents: plasma glucose and insulin levels are lower, insulin sensitivity is improved, body temperature is lower, and age-associated DHEA-S declines less rapid. Nevertheless, studies in human populations are sparse, and it is unclear whether CR mammals in the wild would be able to withstand physiological stressors such as infection, hypothermia and hyperthermia, dehydration, and vigorous exercise (35).

Vallejo performed what may thus far be the only interventional study of a calorically restricted diet, with adequate nutrition, on human mortality. Sixty nonobese elderly men and 60 controls were studied. The CR group was underfed every second day, with mean overall energy intake of approximately 1505 kilocalories per day (6300 kilojoules). This represented an approximate 35% reduction versus the control group. Over the 3-year term of this study, the experimental group suffered fewer deaths and fewer days of illness (36).

Despite this study, our understanding of long-term low energy intake in humans and mortality, under conditions of adequate nutrition, is meager (8). Epidemiological studies suggest that energy balance and BMI are directly related to total mortality and cause-specific mortality (8,10). Increases in cardiovascular mortality (CHD, stroke) as well as mortality from diabetes and certain cancers related to insulin or insulin-like growth factors (e.g., breast, prostate, colon) are correlated with higher BMI and weight gain with age, which reflect a positive energy balance and suggest higher energy intake (8,10,37–39). Difficulty in adequately controlling for physical activity, or energy output, and the difficulty of assessing energy intake in large populations make conclusions much more difficult in humans (8,10,37).

Some support for the CR hypothesis may be seen in the relationship between BMI and mortality. This is controversial since BMI reflects combined effects of caloric intake, physical activity, and body weight/obesity. In the Harvard Alumni Health Study (39) and the Nurses' Health Study (40), mortality from all causes was reduced in study participants with BMIs that were 15% to 20% below the national average. These analyses also controlled for cigarette smoking and illness-related weight loss. In both studies, the group with the lowest BMI (less than 19.0 for women and less than 22.5 for men) had about 20% lower risk of death than those in the group with the next higher BMI (39,40).

In cross-sectional studies of humans in Okinawa, energy intake was found to be 17% lower in adults and 36% lower in children than the average energy intake in Japan, and cardiovascular and cancer mortality rates were up to 40% lower than the national average (11,12). In Sweden, a study of BMI linked high levels of total food intake, energy intake, and prostate cancer risk, a finding that is supported by some, but not all, studies of colorectal, breast, and prostate cancers (41).

Prospective studies in humans have been few, but the physiologic responses of nonobese humans to CR diets resemble the animal findings. For example, human data are available for 8 men and women who were confined inside Biosphere 2 for a 2-year period (42). Energy intake was low (1780 kcal/day) but food quality high. Significant weight loss occurred and was associated with decreases in systolic and diastolic blood pressure, total cholesterol, triacylglycerol, and fasting glucose. Middle-aged men who underwent a CR diet in the Netherlands, with a 20% reduction in the habitual energy intake for 10 weeks, lost 10% of their body weight (43). Changes included lower systolic and diastolic blood pressure, increases in serum high-density lipoprotein cholesterol concentrations, reductions in serum triiodothyronine concentrations and metabolic rate, and positive alterations in fibrinolytic factors (43,44).

A rapidly expanding body of data implicates oxidative stress and insulin signaling as important in the development

of CHD, stroke, cancer, dementia, and other age-related diseases (2,3,27). As noted in animal studies, organs such as the brain and heart, in which the parenchyma consists of postmitotic cells, are particularly susceptible to oxidative damage. Thus, insulin-mediated oxidative stress and damage may be causal factors in senescence, and various diseases associated with aging and energy restriction may attenuate this damage.

Conclusion

Despite the significant limitations of a single 24-hour recall for measuring long-term energy intake, we observed modest direct trends between low energy intake and reduced risk for all-cause mortality in a large, population-based prospective study of men with very long follow-up. This lower risk persisted until energy intake fell to less than 50% of the group mean. This is consistent with observations in animal studies of the mortality benefits of low energy intake until approximately 50% energy restriction. More studies are required to further delineate the effects of low energy intake without malnutrition in humans.

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Address correspondence to Bradley Willcox, MD, Pacific Health Research Institute, 846 South Hotel St., Suite 301, Honolulu, HI 96813. E-mail: bjwillcox@phrihawaii.org

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