Energy expenditure and the obesity epidemic

Dear Sir:

In a recent article, Swinburn et al (1) examine the increasing prevalence of obesity from the perspective of the changes in energy flux with weight gain and assess its etiology in terms of increased energy intake (TEI) as opposed to reduced physical activity (PAEE) and energy expenditure (TEE). They report the relation between body weight (W) and energy flux, defined as TEE = TEI, with TEE measured by doubly labeled water (DLW), in a large cohort of adults. They then show that energy flux exhibits a positive relation with W and argue that “the constraints of the first law of thermodynamics allowed us to infer that a high TEI must be the major driver of higher body weight in modern populations” (p 1724). They then go on to use the exponent of the W vs TEE relation, the slope of the log-transformed regression of W on TEE, to calculate the energy flux gap, the difference in TEE between the 1970s and that of the current, more obese population.

The first of these conclusions about causality can easily be shown to be highly unlikely. The authors argue that if obesity was primarily determined by lower PAEE one would expect that energy flux (TEE) would fall as W increases—ie, the exponent of TEE as a function of W to be negative. On this basis, a strongly positive observed slope means, ipso facto, that a high TEI is the main driver of the high TEE and a high body weight. In fact, to observe an obviously negative exponent of TEE as a function of W given the known current population level of PAEE [a physical activity level (PAL) of 1.65 for large cohorts of mainly overweight and obese US adults (2, 3)], it must have fallen from a level in which the majority of the population was exhibiting the highest sustainable level of PAEE (ie, PAL = 2.5). Simple calculations of TEE from predicted basal metabolic rate (BMR) and PAL values show that even for a modest fall of 10% in TEE, as W increases from a body mass index (BMI; in kg/m²) of 22.5–30, (a greater mean change than has occurred), current PAL values would have to have fallen from a population mean of >2.2. Although the mean population PAL in the 1970s is not known, no one would suggest that at that time a large fraction exhibited maximum sustainable activity levels.

Physiologically, TEE varies as a function of W, and to reverse such causality would cause Kleiber to turn over in his grave. He (4) showed that Voit’s interspecies surface law relating metabolic rate to body surface area was better expressed as a linear relation with weight after log transformation of W and TEE, with the slope being ~0.75—ie, TEE ∝ W⁰.⁷⁵. Within species, TEE also varies with increasing adult weight with an exponent considerably less than 1. This is because for most individuals (PAL < 2) PAEE < BMR, so that BMR is the main driver of the relation between weight and TEE. My calculations from the Dietary Reference Intake (DRI) DLW data set as given in the appendix of the Institute of Medicine’s DRI report (5) show that BEE and TEE vary with weight with very similar exponents of 0.64 (95% CI: 0.60, 0.68; r² = 0.56) and 0.66 (95% CI: 0.59, 0.73; r² = 0.32). PAEE as a percentage of TEE for individuals with PAL values of, for example, 1.5 (sedentary) and 1.8 (healthily active) accounts for 33.3% and 44% of TEE, respectively (ie, the change in PAEE is only 11% of energy expenditure).

Swinburn et al (1) do not report the exponent of TEE as a function of W but report the reverse as W ∝ TEE⁻³⁄₇. This is unlikely to be the same as the reverse relation because reversing dependent and independent variables in regressions often gives different slopes unless the intercept is set to zero because of the partition of variability of regressors between intercept and slope. For example, my calculations with the DRI DLW database show that the exponent of W as a function of TEE is 0.49 (95% CI: 0.44, 0.54) or 0.528 (95% CI: 0.460, 0.596) for the multivariate regression with height, age, and sex as covariates, slopes that are significantly lower than the value of 0.71 obtained for the cohort analyzed by Swinburn et al (1). This raises doubts about the extent of any difference between adults and children examined in a similar fashion by the authors in a previous study (6). However, the magnitude of such a regression coefficient and the calculations performed with it to calculate an energy flux gap has interest only in the context of the logic presented by these authors, which is insecure to say the least.

Indeed, the arguments relating to the concept of an energy flux gap as identified here are unconvincing. In the accompanying editorial, Heymsfield (7) compares the energy gap calculated by Swinburn et al (1) with the much smaller one calculated by Hill et al (7) and by others, but makes the comment that “Comparing estimates is difficult, however, because the nature of evaluated subjects, measured variables, applied assumptions, and even the definition of energy gap varies across these studies” (p 1724). In fact, Swinburn et al (1) discuss 2 energy gap concepts: the energy imbalance gap defined as TEI – TEE, which is sensible and which is what Hill et al (8) attempted to estimate, and an energy flux gap that is essentially TEE large person minus TEE small person. Why define this as a gap? Of course TEE and TEI increase with weight gain, and for substantial weight gain over decades this increase will be greater than the daily energy imbalance gap that mediates the weight change, but so what? It simply represents the increase in BMR as W increases, but tells us nothing about how the increase has occurred. For example, analysis of the relation between BMI and TEE in the DRI DLW database (2) indicates that an increase in BMI from 22.5 to 30 is associated with an increase of 1.3 MJ/d. This is a simple and accurate way of calculating the energy flux gap for this population, if such a value was useful in informing public health policy. A true measure of the population change in TEI would be informative, but currently we cannot measure this. DLW studies inform us about mean TEE for short time periods (usually 2 wk). They provide no true measure of TEI during the measurement period (or at any other time). DLW TEE measurements are only a proxy for habitual TEI if 2 caveats are observed: 1) subjects are in energy balance during the measurement period and 2) behavior (physical activity) during the measurement period is the same as habitual behavior. For the first
of these caveats, only precise measurement of weight change or TEI over the period, if such measurements were possible would inform on whether TEI differed from TEE. Because subjects may be advised to maintain stable weight, or may do this consciously or unconsciously by changing TEI, TEI during the DLW measurement period may differ from habitual energy intakes. As for the second caveat, TEE is known to vary over time because behavior is not constant. Within-subject repeated measurement of TEE by DLW in one report (9) showed a CV of 7.8%, and a CV of 12.6% in another (3), with some individuals exhibiting TEE in the second measurement of only 50% of the first, albeit with at least a year between measurements.

Heymsfield’s editorial (7) concludes that “the report by Swinburn et al (1) and those of others attempting to define the energy gap magnitude, provide us with a rich critical mass of information on which to build newer, more refined, and potentially more flexible models.” This is, in my view, a very generous comment. A key point from the UK Foresight review of the public health implications of obesity (10) was that “disproportionate attention is given to debates over the relative importance of diet or inactivity in the aetiology of obesity, given that the subtle shifts in energy balance which have occurred at a population level are below the limits of detection of current methodologies,” a view that I subscribe to and which was reinforced by the article by Swinburn et al (1).

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Reply to DJ Millward

Dear Sir:

For the most part, our basic conclusions are similar to Millward’s (1), except that we took a mathematical modeling approach whereas he has taken a physical approach. We agree that, although population weight gains could theoretically be due to a drop in physical activity energy expenditure (PAEE), this would need to be so large and uniform as to be physiologically unlikely. We felt that a mathematical approach was important because there are still investigators making inappropriate conclusions about the size of changes of total energy expenditure (TEE) or total energy intake (TEI) leading to, or needed to reverse, obesity.

We made the assumption that across the population on a given day TEE closely equaled TEI and found that energy flux (EnFlux = TEE = TEI) was positively associated with body weight. Millward argues that for a population to exhibit a negative exponent of EnFlux as a function of body weight, a significant proportion of the population would need to have very high PAEE levels. We agree with this but contend that it is plausible that for populations 100 y ago, with sizable proportions of the population who were both lean and very active as a consequence of heavy manual jobs, the relation between EnFlux and body weight could certainly have been flat (ie, no relation). For example, lean men with an average weight of 65 kg doing heavy manual work [up to a physical activity level (PAL) of ~2.2] would have a TEE similar to a group of less-active men weighing ~100 kg.

However, we believe that for the modern population in countries such as the United States, the positive nature of the observed relation between EnFlux and body weight indicates that population increases in body weight will be accompanied by an increase in both TEI and TEE (ie, EnFlux). Conceptualizing how a reduction in PAEE could act as a driver toward a state of higher mean TEE that accompanies the higher weight is a conundrum, so postulating an increase in TEI as the major driver of higher body weight in modern populations seems far more parsimonious and physiologic.

Kleiber certainly placed on the map the fact that TEE varies as a function of weight (especially across species) (2), but both Kleiber and anyone on the street would agree that increasing or decreasing TEE through changes in PAEE would change body weight. Thus, TEE and body weight are clearly codependent. The points that Millward makes about the effects that taking one or the other as the dependent variable has on the coefficient are well made. We have examined this further and reported the equations we derived for adults using log-transformed data with body weight on the x-axis as Ln EnFlux = 0.668 Ln Weight (or 0.521 for the adjusted model) (3). These match the equations that Hall et al (4, 5) derived by using a completely different approach and give confidence that this is the appropriate approach.

Millward questions the differences we found in the EnFlux-weight relation between adults and children. As seen in Figure 5 in our article (1), the fully adjusted population distributions for adults and children are barely overlapping. We show here (Figure 1) the raw data for weight compared with TEE using doubly labeled water (DLW) techniques (n = 963 for children, n = 1399 for adults) (1, 6), and the differences are still apparent.

In our article (1), we identified 2 energy gaps: the first is the small (tens of kJ/d) average gap between TEI and TEE (we called it the energy imbalance gap), which, if continued over decades, leads to 2 outcomes. The obvious one is weight gain, but the less obvious one (at least to nonphysiologists) is this second energy gap (which we called the energy flux gap), which is the average difference in the energy flux between 2 time points. Although one could argue about
the names, the concept is critical, ill-understood, and has profound implications for public health. If our present-day population, with its high prevalence of obesity, is eating and burning substantially more energy (several hundred kJ/d) than the population of 3 decades ago, that represents the size of the public health challenge ahead of us to return to our less obese, former selves. The size of the second gap is not trivial, and our analyses (7) and those of Hall et al (4) strongly suggest that unless interventions address the "push factor" of increased food energy supply and marketing, the obesity epidemic will be very difficult to reverse.

Millward argues that DLW studies provide "no true measure" of TEI because the measurements are associated with random error, and energy balance may be somewhat high or low over the 2-wk measurement period. These statements are technically true, but with large sample sizes these effects tend to balance out across the population, and DLW measurements, although not perfect at the individual level, are the most accurate assessment we have of free-living TEE and TEI and have been shown to be so (8). Also of note are the lower CV values for more recent DLW measurements (5.1%) (9) than are given in the earlier review (10) quoted by Millward. Whereas DLW measurements were not from representative samples of populations, the large sample sizes we used, which included several different ethnic groups, gives us confidence that the physiologic relations we observed are giving us important insights into population TEE, TEI, and mean weight change.

Millward finishes on a note of skepticism that understanding the etiology of the obesity epidemic is fruitless because we have difficulty in measuring the tiny energy imbalance gap. We take a different view, which is that critical analyses of the larger, and more important, energy flux gap and similar analyses (4) can uncover evidence about the drivers of the obesity epidemic. Identifying the etiology of any disease with sharp increases in prevalence or incidence is fundamental to directing prevention efforts toward reducing the underlying drivers of the problem. This is a basic tenet of public health, and one to which we subscribe.

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Dear Sir:

Epidemiologic studies of salt in Asia deserve attention because the Asian population has twice as high an intake of salt as US or European populations (1). Therefore, the articles by Takachi et al (2) and Umesawa et al (3), which appeared in recent issues of the Journal, and any other studies of salt from Asia deserve consideration in future reviews. The report by Takachi et al is particularly important because it included cardiovascular disease (CVD) and cancer as the outcomes. However, at least 2 points should be considered in future reviews.

First, the studies may involve residual confounding of associations of total salt intake with diseases risks. Takachi et al (2) reported that salted-fish consumption was one of the sources of salt and was significantly associated with a 14% lower risk of CVD or a 34% lower risk of myocardial infarction. As discussed by the authors, the findings supported cardioprotective roles of omega-3 polyunsaturated fatty acids (n–3 PUFAs). The authors identified correlations between intakes of salted fish and salt ($r = 0.1–0.3$). The associations between CVD and fish and salt intake indicated that conclusions on the basis of total salt intake were confounded by n–3 PUFA intake.

Similarly, phytoestrogen may be a residual confounder of associations between total salt intake and cancer risks. Other studies that used the Japanese cohort of Takachi et al (2) previously related salt and phytoestrogen to cancer outcomes (4–6). One of the dietary sources of phytoestrogen and salt is miso soup, which is a typical part of the Japanese diet; Takachi et al (2) reported a positive correlation between miso soup and total salt intake ($r = 0.4$). Thus, analyses of associations between total salt and cancer may need adjustment for phytoestrogen intake.

Cumulative observations suggested that n–3 PUFAs and phytoestrogen may confound associations of total salt with chronic diseases in Japan. Notably, 90% of Japanese adults consume $>1.0$ g n–3 PUFAs/d and $>3.0$ g sodium/d, whereas 75% of US adults consume $<0.8$ g n–3 PUFAs/d and $<4.0$ g sodium/d (1, 7). Intakes of phytoestrogen, teas, or other culture-specific foods show similar characteristics. Therefore, Takachi et al and other investigators in Asia should carefully consider covariates for different disease outcomes and mutual confounding by multiple dietary factors.

The second concern about these studies is that their analyses do not take into account their cohort design. The cohorts of Takachi et al (2) and Umesawa et al (3) were from nationwide, multicenter studies, and analyses were often performed without adjustment for the multiple centers. Takachi et al argued that adjustment for regions could have masked associations. However, the attenuation is not necessarily a bias. After adjustment for regions, the authors would be able to obtain more valid results without bias or ecological fallacy due to unmeasured confounders, such as regional socioeconomic environments.

Moreover, the multicenter designs could cause nondifferential misclassification due to the difference in validity of any assessments across regions. In the cohort of Takachi et al (2), amounts of sodium intake, validity of dietary assessments, and disease incidence were different across regions (8, 9). An extreme example of the Japanese study is the consumption of pickled vegetables, which was positively associated with gastric cancer in the study of Takachi et al. In validation analyses, energy-adjusted correlation coefficients for pickled vegetable consumption between dietary records and food-frequency questionnaires ranged from $-0.19$ to $0.49$ across regional

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areas (8). Pooling all individuals without adjustment for regions, the ecological approach reasonably showed a higher correlation coefficient, 0.54 (8). Therefore, with regard to the regional difference in outcomes (2), Takachi et al may have provided results with non-differential misclassification. These issues may be present in other multicenter cohort studies (3), and thus future reviewers should interpret such studies carefully.

In conclusion, studies from Takachi et al (2), Umesawa et al (3), and others undertaking similar analyses may provide results with unadjusted regional and dietary confounding. Additional studies, or even reanalyses of the nationwide cohorts, are needed to provide valid results of associations between salt and diseases. Minimizing such potential biases will allow valid inference about benefits by reducing salt intake without reducing intakes of beneficial nutrients, such as n–3 PUFAs, or without moving across regions. Investigators and reviewers for the Journal should be aware of the aforementioned methodologic issues based on cultural backgrounds and relatively complex study designs.

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Reply to F Imamura

Dear Sir:

In our study (1), we did not adjust for n–3 polyunsaturated fatty acid (PUFA), which is abundant in dried and salted fish, or isoflavones, which are major phytoestrogens in miso soup, because we were concerned that entering the 2 variables into multivariable models would have led to overadjustment due to collinearity. Further adjustment for n–3 PUFA and isoflavones as suggested by Imamura, however, did not change our principal findings materially: original and reanalyzed multivariable hazard ratios (HRs) of total cancer for the highest compared with lowest quintiles were 1.15 (95% CI: 1.04–1.27; P for trend = 0.01) and 1.16 (95% CI: 1.04–1.28; P for trend = 0.01), respectively, for salted fish and 1.04 (95% CI: 0.93–1.16; P for trend = 0.61) and 1.05 (95% CI: 0.93–1.18, P for trend = 0.57), respectively, for soy. Findings for cardiovascular disease (CVD) also showed no material change, with corresponding HRs of 0.86 (95% CI: 0.74–0.99; P for trend = 0.04) and 0.82 (95% CI: 0.70–0.96; P for trend = 0.01), respectively, for dried and salted fish, and 1.19 (95% CI: 1.01–1.40; P for trend = 0.06) and 1.20 (95% CI: 1.01–1.43; P for trend = 0.07), respectively, for sodium.

We usually adjust for study area in Japan Public Health Center–based prospective studies (2) but chose not to do so in this article on the basis that, although the study areas had wide variation in sodium intake, validities of intake were relatively low and different for individual areas, with narrow variations, albeit that they were reasonable for the study as a whole. Differential correlations according to study areas between consumption of sodium or salted foods estimated by our food-frequency questionnaire and those calculated by diet records were chiefly within the range of random variation caused by the relatively small number of subjects in the validation study in each area (n = 51– 61). Furthermore, the correlations were not generally associated simultaneously with regional differences in sodium or salted food intake and with differences in the incidence of total cancer or CVD. It is therefore unlikely that our choice not to adjust for study area resulted in biased observations due to nondifferential misclassification.

We understand that no observational study can perfectly control potential confounding factors and that caution is therefore required in the selection of variables with regard to both biological and statistical considerations. Furthermore, the possibility of residual confounding should always be acknowledged.

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REVIEW
