Report

Current Biology

Constrained Total Energy Expenditure and Metabolic Adaptation to Physical Activity in Adult Humans

Highlights

- We measured total energy expenditure and physical activity in a large adult sample
- Above moderate activity levels, total energy expenditure plateaued
- Body fat percentage was positively related to total energy expenditure
- Activity intensity was inversely related to total energy expenditure

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In Brief

Pontzer et al. examine total energy expenditure and physical activity in a large adult human sample. Rather than increasing linearly with physical activity, total energy expenditure plateaus above moderate activity levels, suggesting that the body adapts to higher activity levels to keep total energy expenditure within a relatively narrow range.

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Constrained Total Energy Expenditure and Metabolic Adaptation to Physical Activity in Adult Humans

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SUMMARY

Current obesity prevention strategies recommend increasing daily physical activity, assuming that increased activity will lead to corresponding increases in total energy expenditure and prevent or reverse energy imbalance and weight gain [1–3]. Such Additive total energy expenditure models are supported by exercise intervention and accelerometry studies reporting positive correlations between physical activity and total energy expenditure [4] but are challenged by ecological studies in humans and other species showing that more active populations do not have higher total energy expenditure [5–8]. Here we tested a Constrained total energy expenditure model, in which total energy expenditure increases with physical activity at low activity levels but plateaus at higher activity levels as the body adapts to maintain total energy expenditure within a narrow range. We compared total energy expenditure, measured using doubly labeled water, against physical activity, measured using accelerometry, for a large (n = 332) sample of adults living in five populations [9]. After adjusting for body size and composition, total energy expenditure was positively correlated with physical activity, but the relationship was markedly stronger over the lower range of physical activity. For subjects in the upper range of physical activity, total energy expenditure plateaued, supporting a Constrained total energy expenditure model. Body fat percentage and activity intensity appear to modulate the metabolic response to physical activity. Models of energy balance employed in public health [1–3] should be revised to better reflect the constrained nature of total energy expenditure and the complex effects of physical activity on metabolic physiology.

RESULTS

Models of Total Energy Expenditure and Physical Activity

The metabolic costs and health benefits of physical activity are well established [1, 2], but the long-term effect of physical activity on total daily energy requirements is far less certain. The predominant view [1–3] assumes a dose-dependent and additive effect of physical activity on total energy expenditure (kcal/day), with each increment of physical activity leading to a corresponding increase in total energy expenditure (Figure 1). This Additive model is supported by studies showing positive correlations between total energy expenditure and accelerometry recordings of physical activity [4]. Moreover, the Additive total energy expenditure model of metabolic physiology has shaped public health strategies to combat the global rise in obesity, which typically propose increasing physical activity as a means to increase total energy expenditure and achieve a healthy weight and maintain energy balance [1–3].

A growing number of studies examining the long-term metabolic effects of exercise suggest that the relationship between physical activity and total energy expenditure is more complex than Additive models allow [5]. Rather than increasing total energy expenditure linearly in response to physical activity, individuals tend to adapt metabolically to increased physical activity, muting the expected increase in daily energy throughput [5, 10–12]. These metabolic changes can be behavioral, such as sitting instead of standing, or fidgeting less, but they may also include reductions in other, non-muscular metabolic activity. For example, men and women enrolled in a long-term exercise study exhibited reduced basal metabolic rate at week 40 [11], and studies in healthy adult women have shown suppressed ovarian activity and lower estrogen production in response to moderate exercise [13]. Other species have also

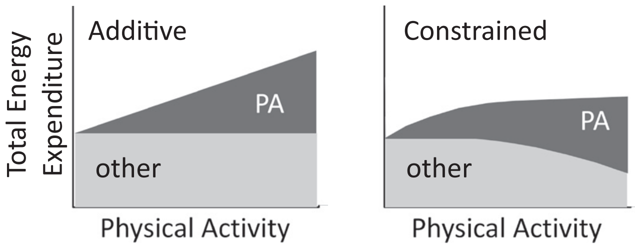

Figure 1. Schematic of Additive Total Energy Expenditure and Constrained Total Energy Expenditure Models

In Additive total energy expenditure models, total energy expenditure is a simple linear function of physical activity, and variation in physical activity energy expenditure (PA) determines variation in total energy expenditure. In Constrained total energy expenditure models, the body adapts to increased physical activity by reducing energy spent on other physiological activity, maintaining total energy expenditure within a narrow range.

been shown to keep total energy expenditure remarkably constant in response to increased physical activity, reducing energy expenditure on growth [14], somatic repair [15, 16], and basal metabolic rate [17, 18] and even reducing lactation and cannibalizing nursing offspring [19], even when food is available ad libitum and total energy expenditure is well within maximum sustained levels [5, 14–19]. These observations are inconsistent with Additive models; instead, they favor a Constrained total energy expenditure model [5] in which energy allocation among physiological tasks responds dynamically to long-term shifts in physical activity, adapting to maintain total energy expenditure within some relatively narrow range (Figure 1).

Constrained total energy expenditure may explain the remarkable degree of similarity in total energy expenditure among populations across a broad range of lifestyles. People in less socioeconomically developed populations, including subsistence farmers and traditional hunter-gatherers, have total energy expenditures similar to those in more developed populations [6, 7] despite substantial differences in physical activity. Mammals living in the wild, including non-human primate species, have total energy expenditures similar to captive populations [8]. These population-level comparisons suggest that total energy expenditure is an evolved, species-specific trait that is homeostatically buffered against variation in habitual physical activity. It remains unclear, however, how the growing evidence for metabolic adaptation and metabolic constraint can be reconciled with accelerometry studies showing a positive correlation between physical activity and total energy expenditure [4]. Missing from these comparisons is an ecological study of total energy expenditure and physical activity collected simultaneously within a large, diverse sample, needed to characterize the relationship between variation in habitual levels of physical activity and total energy expenditure among individuals.

In this study, we evaluated Additive and Constrained total energy expenditure models in a large (n = 332), mixed-sex (55% female), adult (age 25–45 years) human sample [9] drawn from five populations across Africa and North America (Ghana, South Africa, Seychelles, Jamaica, and United States; see Table S1 for sample characteristics). Total energy expenditure was measured using the doubly labeled water method. Resting metabolic rate was measured via respirometry. Physical activity was measured using wearable tri-axial accelerometers (reported as mean counts per minute per day, CPM/d); surveys were used to identify subjects employed in manual labor (Experimental Procedures). First, we used multivariate regression to examine the effects of anthropometric variables, population location, and physical activity on total energy expenditure and resting metabolic rate. We then used residuals from a multiple regression including anthropometrics and population location (Table 1, model 2) to calculate adjusted total energy expenditure and adjusted resting metabolic rate, and to investigate the relationship between physical activity and these size- and population-adjusted measures of expenditure.

Statistical Models of Total Energy Expenditure

Anthropometric measurements explained just over half of the variation in total energy expenditure (df = 326, adjusted r^2 [adj. r^2] = 0.52, $p < 0.001$; Table 1, model 1), with fat-free mass the strongest single determinant. Adding a "study site" term to the model marginally improved the fit (df = 322, adj. $r^2 = 0.55$, $p < 0.001$; Table 1, model 2). Measures of physical activity (accelerometer CPM/d and manual labor employment) accounted for an additional 4% of the variation in total energy expenditure (df = 292, adj. $r^2 = 0.59$, $p < 0.001$; Table 1, model 3). Study site remained significant (Table 1, model 3), indicating that differences in lifestyle among sites had measurable effects on total energy expenditure that were not wholly accounted for by accelerometry, anthropometry, and manual labor employment. Adding the term body weight × CPM/d to model 3, to account for the greater metabolic cost of physical activity for larger individuals, did not affect the fit (adj. r^2) of the model, and the term was not a significant predictor of total energy expenditure ($t(291) = -0.19$, $p = 0.85$). Similarly, substituting body weight × CPM/d for the CPM/d term in model 3 did not affect the fit of the model. Adding measures of time spent in "sedentary" (<100 CPM) and "vigorous" (≥3960 CPM) physical activity improved the fit of the model to adj. $r^2 = 0.61$ (Table 1, model 4).

To examine the effects of physical activity on total energy expenditure, we calculated adjusted total energy expenditure (total energy expenditure_{ADJ}) from the residuals of model 2 in Table 1, thereby controlling for the effects of fat-free mass, fat mass, age, height, sex, and study site on total energy expenditure. Variation in total energy expenditure_{ADJ} with respect to physical activity was substantial; physical activity accounted for only 7% of the variation in total energy expenditure_{ADJ} (Table 1, models 5 and 6). The mean coefficient of variation within CPM/d deciles (14% ± 3%) was equivalent to the difference in mean total energy expenditure_{ADJ} between the 1st and 10th deciles (15%; see Table S2). The range of variation within any decile of CPM/d far exceeded the difference in median adjusted total energy expenditure across the range of CPM/d. Results were similar across a range of approaches to control for potentially confounding effects of body size and other factors, such as employment in manual labor (see Figures S1 and S2).

Size- and Population-Adjusted Total Energy Expenditure and Physical Activity

The effect of physical activity on total energy expenditure_{ADJ} was non-linear, with a plateau in daily energy expenditure over the

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Table 1. Model Parameters for Multivariate Analyses of Total Energy Expenditure and Total Energy Expenditure$_{ADJ}$

Total Energy Expenditure

	Model 1			Model 2			Model 3			Model 4		
	df = 326, adj. r^2 = 0.52, ±SE 383.7, p < 0.001			df = 322, adj. r^2 = 0.55, ±SE 368.2, p < 0.001			df = 292, adj. r^2 = 0.59, ±SE 349.1, p < 0.001			df = 290, adj. r^2 = 0.61, ±SE 341.8, p < 0.001		
Variable	β	±SE	p	β	±SE	p	β	±SE	p	β	±SE	p
(Intercept)	1227.6	622.0	*	347.7	628.7		−37.1	626.2		−166.2	614.4	
Fat-free mass (kg)	46.4	4.7	****	42.2	5.3	****	41.5	5.3	****	40.5	5.2	****
Fat mass (kg)	−5.0	2.5	*	−2.1	2.9		−0.9	2.9		0.4	2.9	
Height (cm)	−6.2	3.7	*	1.3	3.9		1.4	3.8		1.9	3.8	
Age (y)	2.7	3.6		1.8	3.5		0.1	3.6		−1.2	3.5	
Sex (1 = M, 0 = F)	6.5	88.8		−14.4	95.2		60.2	95.5		39.9	94.0	
Site: Ghana[a]				–	–		–	–		–	–	
Site: Jamaica				−374.0	73.6	****	−269.2	73.7	****	−273.1	73.3	****
Site: South Africa				−164.0	77.6	**	−122.5	76.4		−111.2	76.4	
Site: Seychelles				−100.8	73.1		−39.7	78.6		−56.8	78.9	
Site: USA				−245.6	76.7	***	−181.1	80.7	**	−182.3	83.0	**
CPM/d							1.1	0.2	****	1.4	0.3	****
Manual labor							117.2	47.1	**	114.2	46.2	**
Sedentary PA										1.7	0.6	***
Vigorous PA										−18.1	7.5	**

Total Energy Expenditure$_{ADJ}$

	Model 5			Model 6			Model 7			Model 8		
	df = 330, adj. r^2 = 0.07, ±SE 349.3, p < 0.001			df = 301, adj. r^2 = 0.07, ±SE 348.3, p < 0.001			df = 300, adj. r^2 = 0.09, ±SE 345.2, p < 0.001			df = 298, adj. r^2 = 0.13, ±SE 338.0, p < 0.001		
Variable	β	±SE	p	β	±SE	p	β	±SE	p	β	±SE	p
(Intercept)	2309.0	38.4	****	2277.0	45.1	****	2094.2	84.9	****	1930.1	94.3	****
CPM/d	0.9	0.2	****	0.8	0.2	****	1.0	0.2	****	1.4	0.2	****
Manual labor				100.5	40.5	**	104.4	40.2	**	104.2	39.4	***
Body fat %							4.5	0.03	**	5.2	1.7	***
Sedentary PA										1.7	0.6	***
Vigorous PA										−17.2	7.2	**

Residuals from model 2 were used to calculated total energy expenditure$_{ADJ}$. CPM/d, counts per minute per day. See Experimental Procedures for definitions of sedentary and vigorous physical activity (PA). ****p < 0.001, ***p 0.001–<0.01, **p 0.01–<0.05, *p 0.05–0.10. See also Figure S2 and S3 and Tables S1 and S3.

[a]Ghana is the reference population; values for the other site populations refer to deviations from the Ghana baseline.

upper four deciles (60^{th}–100^{th} percentile) of CPM/d (Figure 2A). This plateau was evident in the lowess regression and in the change in median total energy expenditure$_{ADJ}$ over the range of CPM/d deciles (Figure 2A). The slope of the lowess regression decreases markedly above 200 CPM/d, such that above 219 CPM/d, each additional increment of 100 CPM/d is associated with less than 50 kcal/day increase in total energy expenditure$_{ADJ}$. We used two approaches to determine the activity level above which the effect of physical activity on total energy expenditure$_{ADJ}$ was negligible.

First, we iteratively removed subjects at low CPM/d values and evaluated the effect of physical activity for subjects above increasing CPM/d thresholds (Experimental Procedures). Figure 2B shows the effect (β) of CPM/d on total energy expenditure$_{ADJ}$, in a model including manual labor, at increasing CPM/d thresholds. For the n = 143 subjects above a threshold of CPM/d = 176, the effect of CPM/d on total energy expenditure$_{ADJ}$ is non-significant, and its SE includes zero (β = 0.31 ± 0.32, p = 0.33; Figure 2B). For the n = 99 subjects above a threshold of CPM/d = 216, a model including both CPM/d and manual labor fails to achieve significance (adj. r^2 = 0.02, p = 0.12). There was no measurable effect of physical activity on total energy expenditure$_{ADJ}$ above this threshold.

Second, we used change-point regression to estimate the CPM/d value at which the slope of total energy expenditure$_{ADJ}$ on CPM/d changes from positive to zero (Experimental Procedures). The change point was 230 CPM/d (95% confidence interval 44–428), consistent with the iterative CPM/d threshold analysis (Figures 2A and 2B). For the n = 92 subjects above the change point, the relationship between physical activity and total energy expenditure$_{ADJ}$ is indistinguishable from zero (slope: 0.21 ± 0.35; p = 0.54). The change-point regression also captured a marginally greater amount of variance in total energy expenditure$_{ADJ}$ (df = 304, adj. r^2 = 0.09, p < 0.001) than linear regression did (adj. r^2 = 0.07, p < 0.001, Table 1, models 5 and 6).

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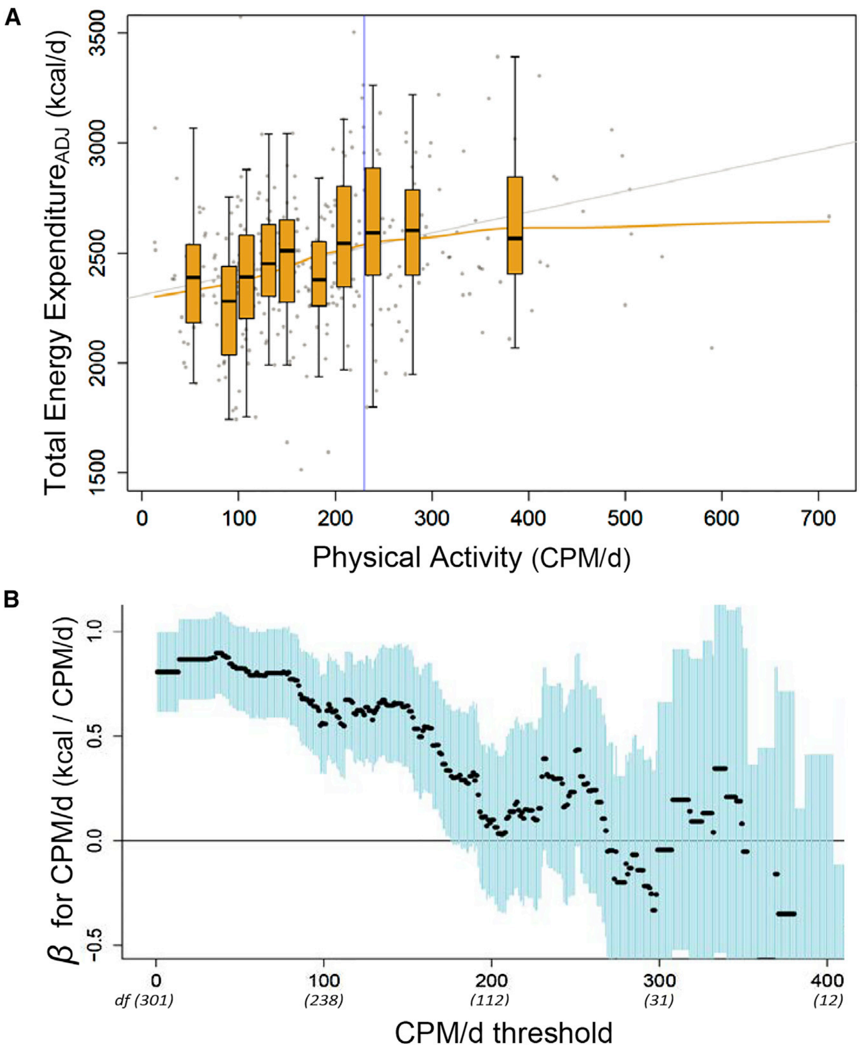

Figure 2. The Relationship between Total Energy Expenditure and Physical Activity in the METS Sample

(A) Total energy expenditure$_{ADJ}$ (kcal/d) and physical activity (CPM/d) in the METS sample. Boxplots indicate medians and quartiles of total energy expenditure$_{ADJ}$ for each decile of CPM/d and are centered on the median CPM/d value for each decile. Lowess (yellow) and ordinary least-squares (gray) regression lines are shown. The change point (230 CPM/d) for the change-point regression, indicated by the vertical blue line, marks the activity level at which the slope of the total energy expenditure$_{ADJ}$:CPM/d regression becomes indistinguishable from zero. Total energy expenditure$_{ADJ}$ values for three subjects exceed 3500 and are not shown; see Figure S1C. See also Table S2 and Figures S1 and S3.

(B) The effect of CPM/d on total energy expenditure$_{ADJ}$ for subjects above increasing CPM/d thresholds. Black dots show the β value for CPM/d for subjects above a given CPM/d threshold; blue bars represent ±SE. Analyses include manual labor. Degrees of freedom (df) are given for major CPM/d thresholds.

Resting Metabolic Rate and Activity Energy Expenditure

To further investigate metabolic response to variation in habitual physical activity levels, we examined two components of total energy expenditure$_{ADJ}$: adjusted resting metabolic rate (resting metabolic rate$_{ADJ}$) and adjusted activity energy expenditure (activity energy expenditure$_{ADJ}$). Activity energy expenditure$_{ADJ}$ was calculated as (0.9 × total energy expenditure$_{ADJ}$ − resting metabolic rate$_{ADJ}$). Resting metabolic rate$_{ADJ}$ was not correlated with physical activity ($t(202) = -0.14$, $\beta = -0.02 \pm 0.11$, $p = 0.89$; Figure 3A). Like total energy expenditure$_{ADJ}$, activity energy expenditure$_{ADJ}$ increased over the low and middle range of physical activity but plateaued above ~230 CPM/d (Figure 3A). Notably, the activity energy expenditure$_{ADJ}$ versus physical activity regression had a significantly non-zero intercept (621.8 ± 44.3, $t(202) = 14.0$, $p < 0.001$). That is, activity energy expenditure$_{ADJ}$, the component of total energy expenditure generally thought to reflect physical activity, was estimated at ~600 kcal/d (~27% of total energy expenditure) when physical activity assessed by accelerometry was 0 CPM/d. The intercept remains significantly greater than zero (545.7 ± 76.4, $t(145) = 5.27$, $p < 0.001$) even when the analysis is limited to subjects with physical activity values below the 230 CPM/d plateau point, where the activity energy expenditure$_{ADJ}$ versus physical activity slope is greatest. Similar results were obtained when examining raw (i.e., unadjusted) total energy expenditure, resting metabolic rate, and activity energy expenditure values, and for a range of models controlling for effects of body size and composition (see Supplemental Experimental Procedures).

We modeled two components of activity energy expenditure (Figure 3B). Activity energy expenditure$_1$ is the component directly linked to physical activity in a dose-dependent manner and is calculated using the slope of the activity energy expenditure versus physical activity regression for CPM/d < 230 (Figure 3A). When CPM/d = 0, activity energy expenditure$_1$ = 0, and each increment of physical activity incurs a corresponding increase in activity energy expenditure$_1$. Activity energy expenditure$_2$ is the remainder of activity energy expenditure, calculated by subtracting activity energy expenditure$_1$ from activity energy expenditure. Activity energy expenditure$_2$ decreases with physical activity above 230 CPM/d, absorbing increases in activity energy expenditure$_1$ while total energy expenditure plateaus (Figure 3B).

DISCUSSION

Metabolic Response to Variation in Habitual Physical Activity

Our analyses of total energy expenditure and physical activity support a Constrained total energy expenditure model. Rather than increasing linearly, in the dose-dependent manner predicted by Additive total energy expenditure models, the

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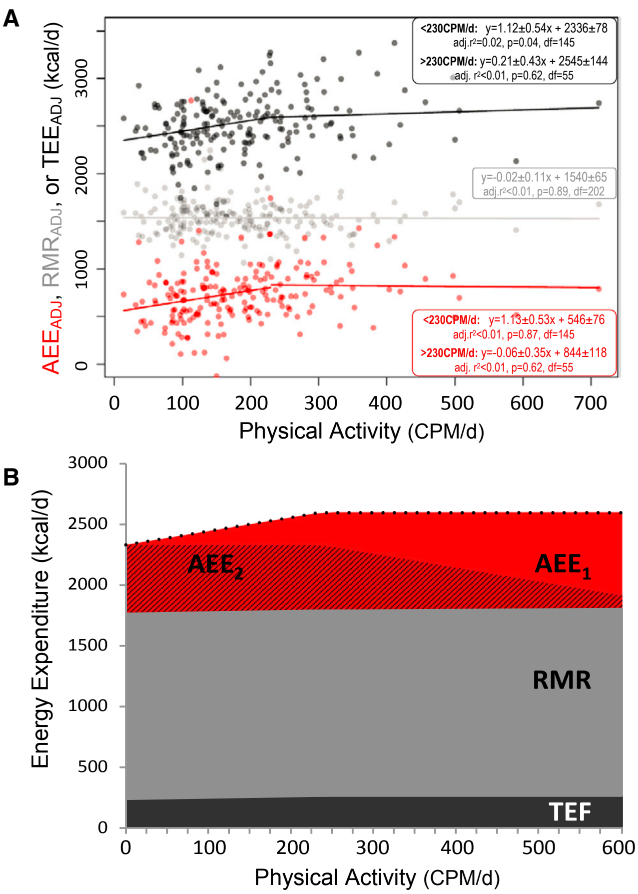

Figure 3. The Effect of Physical Activity on Total Energy Expenditure and Its Components

(A) Total energy expenditure$_{ADJ}$, resting metabolic rate$_{ADJ}$, and activity energy expenditure$_{ADJ}$ (kcal/d) versus physical activity (CPM/d) for the subset of subjects (n = 204) with measured resting metabolic rate. Ordinary least-squares regressions are shown. Resting metabolic rate$_{ADJ}$ is not correlated with physical activity, nor are total energy expenditure$_{ADJ}$ or activity energy expenditure$_{ADJ}$ among subjects with physical activity above 230 CPM/d.

(B) Components of total energy expenditure (dotted line) modeled as a function of physical activity, using relationships shown in (A). Resting metabolic rate is constant (1540 kcal/d). Below the change point of 230 CPM/d, total energy expenditure = 1.12 CPM/d + 2336; above 230 CPM/d, total energy expenditure is constant (2600 kcal/d). The thermic effect of food (TEF) is calculated as 10% total energy expenditure. Activity energy expenditure (red), calculated as (0.9 × total energy expenditure − resting metabolic rate), is divided into two components. Activity energy expenditure$_1$ (AEE$_1$, solid red) increases with physical activity in a dose-dependent manner as 1.13CPM/d, the slope of the adjusted energy expenditure versus physical activity regression for subjects below 230 CPM/d in (A). Activity energy expenditure$_2$ (AEE$_2$, hatched red) is the remainder of activity energy expenditure, calculated as activity energy expenditure$_2$ = activity energy expenditure − activity energy expenditure$_1$. See also Figures S1 and S3.

relationship between physical activity and total energy expenditure$_{ADJ}$ plateaued over the upper range of CPM/d, representing n = 92–99 subjects, roughly 30% of the dataset (Figures 2 and 3; Table S2). Although physical activity must incur an immediate energy cost (activity energy expenditure$_1$), compensatory changes in energy expended on other activities (activity energy expenditure$_2$) apparently negated the additive effect of additional physical activity on total energy expenditure among individuals above ∼230 CPM/d.

The physiological activities comprising activity energy expenditure$_2$, and adapting to high levels of habitual physical activity, are not immediately evident. One hypothesis is that activity energy expenditure$_2$ reflects muscle activity that is not readily recorded via accelerometry (e.g., postural efforts against gravity, fidgeting). These activities have been shown to contribute substantially to total energy expenditure [20–22], and their reduction may contribute to metabolic adaptation [23]. However, the magnitude of activity energy expenditure$_2$ for sedentary subjects (∼600 kcal/d) exceeds the estimated daily cost of standing, fidgeting, and peripheral limb movement [20–22] that would be missed using our accelerometry protocol, suggesting that muscular activity alone cannot account for activity energy expenditure$_2$.

We hypothesize that non-muscular physiological activity contributes substantially to activity energy expenditure$_2$ and its adaptation to physical activity. Human studies and non-human animal models show that energy allocation across a broad range of physiological tasks, including reproductive activity and somatic maintenance [5, 13–19], may be reduced when physical activity increases, resulting in decreased activity energy expenditure$_2$. Indeed, such physical activity-induced reduction in activity energy expenditure$_2$ could potentially contribute to the beneficial health effects of exercise, reducing energy expenditure on inflammation and detrimental immune system activity [24]. Non-muscular contribution to activity energy expenditure$_2$ could also explain why inactive subjects confined to bed rest exhibit physical activity levels (i.e., the ratio of total energy expenditure/basal metabolic rate) of 1.2–1.4, above the value of 1.1 predicted by Additive total energy expenditure models [25].

The mechanisms determining the total energy expenditure set point and regulating activity energy expenditure$_2$ in response to physical activity and the specific changes in energy expenditure are a critical target for future research. Food availability, and particularly the ratio of food availability to physical activity, may be an important developmental signal in determining an individual's total energy expenditure set point [5]. In support of this hypothesis, subjects with greater body fat percentage, which can be considered a long-term signal integrating food energy availability and habitual physical activity, exhibited marginally higher total energy expenditure$_{ADJ}$ across all physical activity levels (Table 1, models 7 and 8; see Figure S3). Activity intensity may also play a signaling role, given the positive and negative effects of sedentary and vigorous activity bouts, respectively, on total energy expenditure (Table 1, models 4 and 8). Activity intensity could potentially modulate activity energy expenditure$_2$ via its effect on fatigue, for example by promoting postural behaviors that save energy (e.g., sitting instead of standing; see [23]), or via myokine signaling [26].

Limitations

One important limitation of this study is its cross-sectional design. Although the available data from prospective studies support a Constrained total energy expenditure model [5], it would be useful to investigate the relationships between total energy expenditure and physical activity examined here within subjects as physical activity was increased over several months, in a longitudinal design. Furthermore, as discussed above, accelerometry is an imperfect measure of physical activity and energy expended in physical activity, which undoubtedly adds to the variance in total energy expenditure$_{ADJ}$ with respect to physical activity (Figures 1A and S3). Another limitation is the absence of resting metabolic rate measurements for subjects at the Jamaica study site, which reduces the sample size for calculating resting metabolic rate and activity energy expenditure. We also lack measurements of the thermic effect of food and must rely on estimates here for calculating activity energy expenditure. Finally, we lack biomarker data to test hypotheses regarding the role of non-muscular physiological activity in modulating activity energy expenditure$_2$.

Bridging Ecological and Experimental Studies of Total Energy Expenditure

The Constrained total energy expenditure model evaluated here provides a unifying framework for seemingly contradictory results from previous studies examining physical activity and total energy expenditure. For studies with large samples that include both high- and low-physical-activity individuals [4], physical activity is expected to have a significant positive effect on total energy expenditure due to the effect of physical activity on total energy expenditure in low- to moderate-physical-activity individuals (Figure 2). Similarly, intervention studies that increase physical activity in sedentary subjects are expected to see an increase in total energy expenditure, at least over the short term (~20 weeks; [5, 10–12]). However, metabolic adaptation to long-term changes in physical activity will blunt the relationship between habitual physical activity levels and total energy expenditure. As a result, comparing industrialized populations with more active traditional populations [6, 7], or animal populations in the wild with those in captivity [8], may not reveal differences in total energy expenditure despite clear differences in physical activity.

The relationship between physical activity and total energy expenditure demonstrated in the large, diverse human sample here is both more variable and more complex than current Additive total energy expenditure models allow. Regardless of the preferred statistical model, physical activity accounts for only ~7%–9% of the variation in total energy expenditure after controlling for anthropometric variables and population location. Energy balance models focusing solely on the effect of physical activity on total energy expenditure while ignoring the interdependent and dynamic role of other organ systems will miss a large portion of the variation in daily energy requirements and may provide a biased measure of total energy expenditure. As shown here, Additive total energy expenditure approaches will tend to underestimate the effect of physical activity on total energy expenditure at low to moderate levels of activity and overestimate the effect of physical activity at higher activity levels (Figure 2B). Furthermore, using activity energy expenditure or the ratio of total energy expenditure/basal metabolic rate (i.e., physical activity level) to assess physical activity will overestimate energy expenditure on activity for subjects at habitually low physical activity levels by pooling activity energy expenditure$_1$ with activity energy expenditure$_2$ (Figure 3), which we suggest includes non-muscular physiological activity. Adopting a Constrained total energy expenditure model for physical activity [5] and parsing activity energy expenditure into activity energy expenditure$_1$ and activity energy expenditure$_2$ will improve the accuracy of energy balance models and advance public health strategies for mitigating the global epidemic of metabolic disease.

EXPERIMENTAL PROCEDURES

Data Collection

Subjects were enrolled as part of the Modeling the Epidemiological Transition Study (METS) [9]. Institutional permissions and subjects' informed consent were obtained prior to data collection. Height and weight were measured using a stadiometer and digital scale, respectively, and self-reported age was recorded. Total energy expenditure was measured for each subject for 7 days using the doubly labeled water (DLW) method [27]. Subjects ingested 1.8 g 10% $H_2{}^{18}O$ and 0.12 g 99.9% ^2H_2O per kg body water. Urine samples collected prior to dosing, 4 hr after dosing, and 7 days after dosing were analyzed for isotope enrichment at the Stable Isotope Core Laboratory at University of Wisconsin–Madison. CO_2 production was calculated using Equation 6.6 in [27], and energy expenditure was calculated using the modified Weir equation, with respiratory exchange ratio determined from dietary records. Surveys were used to identify subjects employed in manual labor.

Resting metabolic rate was measured via respirometry (MaxIIa indirect calorimeter, AEI Technologies; SensorMedics, Viasys Healthcare) in the morning, after an overnight fast. Subjects were supine during resting metabolic rate measurements, which lasted 30 min. Both oxygen consumption and CO_2 production were monitored; data from the first 10 min of each measurement were discarded. Due to equipment failure, resting metabolic rate data from the Jamaica study site had to be discarded prior to analysis; Jamaican subjects are not represented in resting metabolic rate or activity energy expenditure analyses here.

Physical activity was measured using wearable tri-axial accelerometer (Actical, Philips Respironics) [9]. Subjects were asked to wear the accelerometers continuously for 8 days coinciding with total energy expenditure measurement, and to remove the devices only for swimming, showering, or bathing. Days were considered valid for analysis only if the devices were worn $\geq$62% of maximal available wear time, and subjects were only included in analyses of physical activity if they recorded a minimum of 4 valid days. Wear time did not covary with measured physical activity levels: there were no differences among the deciles of physical activity (CPM/d) in wear time (ANOVA: $F(9,322) = 0.423$, $p = 0.922$)). For analyses of physical activity intensity (Table 1, models 4 and 8), physical activity was defined as "sedentary" (<100 CPM) or "vigorous" ($\geq$3960 CPM) using published cut points [28, 29]. Following the National Center for Health Statistics [30], "sedentary" and "vigorous" physical activity intensity (Table 1, models 4 and 8) is the total time in minutes accumulated in 10-min intervals. Following prior conventions, we allowed for up to 2 min of below- or above-threshold count activity before considering the bout to be ended [30].

Data Analysis

We analyzed the association between total energy expenditure and physical activity, assessed via accelerometry as mean counts per minute per day (CPM/d), using several approaches. We began by using multivariate regression to investigate the relative effects of anthropometric variables (fat-free mass, fat mass, height, age, and sex) and behavioral or lifestyle variables (accelerometry CPM/d, employment in manual labor, and location) on total energy expenditure, using linear regression in R [31]. By far the strongest anthropometric correlate of total energy expenditure was fat-free mass; fat mass and height were marginally negatively correlated with total energy expenditure, and age and sex had no effect (Table 1, model 1). To examine the effect of physical activity on total energy expenditure while controlling for anthropometric effects, we calculated adjusted total energy expenditure, total energy expenditure$_{ADJ}$, for each subject by adding residuals from the total energy expenditure ~ fat-free mass + fat mass + height + age + sex + study site regression to mean total energy expenditure (model 2 in Table 1; see Supplemental Experimental Procedures). Total energy expenditure$_{ADJ}$ was used for subsequent analyses in the main text. We similarly calculated an adjusted resting metabolic rate, resting metabolic rate$_{ADJ}$, by adding residuals from the resting metabolic rate ~ fat-free mass + fat mass + height + age + sex + study site regression to mean resting metabolic rate, and we calculated an adjusted activity energy expenditure, activity energy expenditure$_{ADJ}$, as (0.9 × total energy expenditure$_{ADJ}$ − resting metabolic rate$_{ADJ}$). We also tested a range of other models correcting for anthropometric and other effects on total energy expenditure and resting metabolic rate, as well as raw (unadjusted) values of total energy expenditure, resting metabolic rate, and activity energy expenditure; results were nearly identical to those reported in the main text (see Supplemental Experimental Procedures and Figures S1 and S2).

To examine the shape of the relationship between physical activity and total energy expenditure and compare Additive and Constrained total energy expenditure models, we fit three different regression models to the scatterplot of total energy expenditure$_{ADJ}$ against CPM/d. First, we fit a robust locally weighed regression (lowess) curve [32] using the "lowess" function in R [31], with f = 2/3, iter = 5. This nonparametric model allows studying non-linear relationships between continuous variables (e.g., physical activity and total energy expenditure) without assumptions about the shape of the underlying function. Second, to test the fit of a linear, Additive total energy expenditure model, we estimated the linear correlation, via Pearson's correlation coefficient, between total energy expenditure$_{ADJ}$ and physical activity (Table 1, models 5 and 6). We used a modified version of this approach for the CPM/d threshold analysis (Figure 1B): we evaluated the effect of CPM/d and manual labor on total energy expenditure$_{ADJ}$ via linear regression for all subjects with CPM/d values above a threshold CPM/d = i and iterated this analysis over the range of CPM/d thresholds i = (1, 2, 3…500). The resulting set of β, SE, and model adjusted r^2 values were examined with respect to CPM/d threshold (Figure 1B). Lastly, we used change-point regression to estimate the association between physical activity and total energy expenditure$_{ADJ}$, controlling for manual labor employment. This model is similar to the Constrained total energy expenditure model, which predicts a plateau in the physical activity:total energy expenditure relationship at higher activity levels (Figure 1) and allows the estimation of a change point, from increasing linear/additive to flat/plateau. The change point was estimated using a computer-intensive grid search approach [33], which has been shown to more flexible than the standard method based on maximum-likelihood estimation [34]. Bootstrap simulations were applied to calculate the SE of the change-point estimator [35]. We applied an F-like test, based on an approximate permutation test, using a computer-intensive algorithm as described in the literature to formally test whether the Constrained total energy expenditure model (piecewise regression model) was preferred over the Additive total energy expenditure model (traditional linear regression) [36].

SUPPLEMENTAL INFORMATION

Supplemental Information includes three figures, three tables, and Supplemental Experimental Procedures and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2015.12.046.

AUTHOR CONTRIBUTIONS

H.P., L.R.D., and A.L. conceived the study. L.R.D., J.P.-R., P.B., T.E.F., E.V.L., and A.L. collected data. H.P., R.D.-A., L.R.D., R.S.C., D.A.S., and A.L. analyzed data. H.P., R.D.-A., L.R.D., P.B., R.S.C., D.A.S., and A.L. wrote the manuscript.

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