Daily Energy Expenditure through the Human Life Course

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Abstract: Total daily energy expenditure, TEE (MJ/d), is a critical variable in human health and physiology. Previous large-scale studies of daily expenditure have been limited basal energy expenditure, BEE (MJ/d), the minimum requirements of the organs at rest. Here, we analyze a large, globally diverse database of TEE measurements by the doubly labeled water method for males and females aged 8 days to 95 yr. We show that TEE is most strongly related to fat free mass (FFM), and identify four distinct metabolic life stages. FFM- and fat mass-adjusted TEE accelerates in neonates (0-1yr), is elevated throughout childhood and adolescence (1-20 yr), remains stable in adulthood (20-60 yr) even through pregnancy, and declines in older adults (60+ yr). The trajectory of TEE appears to reflect changes in organ size, physical activity, and cellular activity over the lifespan.

One Sentence Summary: Expenditure fluctuates as we age, reflecting changes in behavior, anatomy, and cellular activity.

Main Text: Changes in daily energy demands as we grow, mature, and senesce have been the focus of metabolic research since the field's origins over a century ago (*1*,*2*). Yet we know surprisingly little about the determinants of TEE and its changes over the lifespan. Large (n > 1,000) analyses of human energy expenditure have been limited to laboratory measures of BEE (*3*), which accounts for only a portion (usually ~55%) of TEE, or have relied upon estimates of TEE based on BEE and daily physical activity (*4*). Measurements of TEE in humans during daily life, outside of the laboratory, were not feasible until the 1980's with the advancement of the doubly labeled water (DLW) method which uses stable isotopes (^{2}H, ^{18}O) to calculate the rate of CO_2 production and thus TEE (*5*-*7*). The DLW method has become the gold-standard method for measuring TEE in free-living subjects (*8*), but the largest analyses of TEE to date have been limited in sample size (n < 600), geographic and socioeconomic representation, and/or age (*9-14*). Further, while the proportions of fat mass and FFM are known to affect energy expenditure, large studies of both BEE and TEE have often focused only on total body weight (*3*,*9*), which can conflate effects of age and age-related changes in body composition.

TEE, FFM, and physical activity (PA) change over the life course, often in concert, making it difficult to isolate the effects of size, PA, or cellular activity. TEE increases with age as children grow (*10*), but the relative effects of increasing PA (*15-17*) and age-related changes in tissue-specific metabolic rates, as have been reported for the brain (*18*), are unclear. TEE and BEE increase from childhood through puberty, but much of this increase is attributable to increased FFM, and the role of endocrine or other effects on cellular activity is uncertain (*14*). The decline in TEE beginning in the sixth decade of life corresponds with a decline in FFM (*11*) and physical activity level, PAL (TEE/BEE), but may also reflect cellular senescence.

In this study, we investigated the effects of age, body composition, and sex on TEE and its components, using a large (n = 6,421), geographically and economical diverse (n = 29 countries) database of DLW measurements of females (64%) and males (36%) eight days to 95 years old (*19*). BEE, measured *via* indirect calorimetry, was available for a subset (n = 2,008) and was used to calculate activity energy expenditure, AEE, as (0.9TEE – BEE) (Methods; Table S1). The database currently lacks measures of BEE for subjects < 2 y and includes few pregnant or nursing mothers. We therefore augmented the dataset with published meaures of BEE in neonates and TEE in pregnant and post-partum women (Methods).

TEE, BEE, and AEE increased with FFM in a power-law manner ($TEE = 0.677FFM^{0.708 \pm 0.004}$; Figures 1, S1, S2, Table S1), requiring us to adjust for weight in comparisons of expenditure across subjects and cohorts. With an exponent < 1, the ratio of expenditure/mass does not adequately control for body size because the ratio of MJ/kg will trend lower for larger individuals (Figure S1; *20*). Instead, we used regression analysis (*20*). A general linear model with *ln*-transformed values of energy expenditure (TEE or BEE), FFM, and fat mass in adults 20 – 60 y (Table S2) was used to calculate residual energy expenditures for each subject. We converted these residuals to adjusted expenditures for clarity in discussing age-related changes: 100% indicates an expenditure that matches the expected value given the subject's FFM and fat mass, 120% indicates an expenditure 20% above expected, *etc*. (Methods). Using this approach, we also calculated the portion of adjusted TEE attributed to BEE (Figure 2D; Methods). Segmented regression analysis of (Methods) revealed four distinct phases of adjusted (or residual) TEE and BEE over the lifespan. This pattern was unchanged in analyses of residuals rather than adjusted expenditures.

Neonates (0 – 1 y): Neonates in the first month of life had adjusted TEE of 99.0 ± 17.2% (n = 35) and adjusted BEE of 78.1 ± 15.0% (n = 34; Figure 2). Both measures increased rapidly in the first year of life. In segmented regression analysis, adjusted TEE rose 84.7% per year (95% CI: 70.7, 98.7%) from birth to a break point at 0.7 years (95% CI: 0.6, 0.8); a similar rise (75.5%, 95% CI: 64.6, 84.5) and break point (1.0, 95% CI: 0.9, 1.1) were evident in adjusted BEE. For subjects between 9 and 15 months, adjusted TEE was 146.4 ± 30.6% (n = 43), and adjusted BEE was 147.2 ± 10.6% (n = 167).

Juveniles (1 – 20 y): TEE and BEE, along with FFM, continued to increase with age throughout childhood and adolescence (Figure 1), but adjusted expenditures steadily declined. Adjusted TEE declined at a rate of -2.8% per year (95% CI: -2.9, -2.6%) from 147.8 ± 22.6% for subjects 1 – 2 y (n = 102) to 102.7 ± 18.1% for subjects 20 – 25 y (n = 314; Table S2). Segmented regression analysis identified a breakpoint in adjusted TEE at 20.5 y (95% CI: 19.8, 21.2), after which it plateaued at adult levels (Figure 2). A similar decline (-3.8, 95% CI: -4.2, -3.3) and break point (18.0, 95% CI: 16.8, 19.2) was evident in adjusted BEE (Figure 2, Text S1). No pubertal increases in adjusted TEE or BEE were evident among subjects 10 – 15 y. In multivariate regression for subjects 1 to 20 y, males had a higher TEE and adjusted TEE (Tables S2, S3).

Adults (20 – 60 y): TEE, BEE, and FFM were all stable from age 20 to 60 (Figure 1, 2; Tables S1, S2; Text S1). Sex had no effect on TEE in multivariate models with FFM and fat mass, nor in analyses of adjusted TEE (Tables S2, S4). Adjusted TEE and BEE were stable even during pregnancy, the elevation in daily expenditure matching the expected increase from the gain in FFM and fat mass (Figure 2C). Segmented regression analysis identified a break point at 63.0 y (95% CI: 60.1, 65.9), after which adjusted TEE begins to decline. This break point was somewhat earlier for BEE (46.5, 95% CI: 40.6, 52.4), but the relatively small number of BEE values for 45 – 65 y (Figure 2D) reduces our precision in determining the BEE break point.

Older adults (>60 y): At ~60 y, TEE and BEE begin to decline, along with FFM and fat mass (Figures 1, S3, Table S1). The decline in expenditure is not only a function of reduced FFM and fat mass, however. Adjusted TEE declined by -0.68% per year (95% CI: -0.79, -0.57), and adjusted measures of BEE and AEE fell at similar rates (Figure 2, Figure S3, Text S1). For subjects in their nineties, FFM- and fat mass-adjusted TEE was 74.0 ± 11.6%, ~26% below that of middle-aged adults.

In addition to providing empirical measures and predictive equations for TEE from infancy to old age (Tables S1, S2), our analyses bring to light major changes in metabolic rate across the life course. The stability of adjusted TEE and BEE at ~100% during pregnancy

(Figure 2B) suggests that the growing fetus maintains a FFM- and fat mass-adjusted metabolic rate similar to adults, which is consistent with adjusted TEE and BEE of neonates (both ~100%; Figure 2) in the first weeks after birth. After rapid acceleration in TEE and BEE during the first year, early life is characterized by substantially elevated FFM- and fat mass-adjusted expenditures relative to adults, reflecting elevated nutritional requirements during growth. Declining adjusted TEE through childhood and adolescence may heighten the risk of unhealthy weight gain and compound the challenges of addressing juvenile obesity. Adult expenditures, adjusted for FFM and fat mass, are remarkably stable. Declining metabolic rates in older adults could increase the risk of weight gain, although we did not observe an increase in fat mass or percentage in this period (Figure S3).

Following previous studies (*21-25*), we calculated the effect of organ size on BEE over the lifespan (Methods). At rest, the mass-specific metabolic rates of the heart, liver, brain, and kidneys are much greater than those of the muscles and other lean tissue or fat (*21-25*). Due to the greater proportion of metabolically active organs in early life, estimated BEE from organ size follows a power-law relationship with FFM, with elevated BEE/FFM in infants and children, roughly consistent with observed BEE (Methods, Figure S6). However, observed BEE exceeds organ-based estimates by ~30% in early life (1 – 20 y) and is ~20% lower than organ-based estimates in subjects over 60 y (Figure S6), consistent with previous work indicating that tissue-specific metabolic rates are elevated in children and adolescents (*1*,*22*,*25*) and reduced in older adults (*21*,*23*,*24*).

We modeled the contributions of PA and changes in cellular metabolism over a range of scenarios (Methods). AEE was modeled as a function of PA and body mass, assuming larger indivduals expend more energy during activity. PA could either remain constant at adult levels over the lifespan or follow the trajectory of PA measured *via* accelerometry, which peaks between 5 – 10 y, declines rapidly through adolescence, and then declines more slowly beginning at ~40 y (*15,26,27*). Similarly, BEE was modeled as a power function of FFM (consistent with organ-based BEE estimates; Methods) multiplied by a "cellular metabolism" term, which could either remain constant at adult levels across the lifespan or follow the trajectory observed in adjusted BEE, which peaks ~1 y and declines to adult levels at ~20 y, then declines again in late adulthood (Figure 2). For each scenario, we calculated absolute and adjusted expendtures from observed FFM and fat mass for each age cohort in Table S1 (Methods).

Models that hold PA or cellular metabolism constant over the lifespan do not reproduce the observed patterns of age-related change in absolute or adjusted measures of TEE, BEE, and AEE (Figure 3). Only when age-related changes in PA and cellular metabolism are included does model output match observed expenditures, indicating that variation in both PA and cellular metabolism contribute to TEE and its components across the lifespan. Elevated expenditures in early life may be related to growth or development (*18*,*22*), and the decline in later life may reflect cellular senescence or reduced cellularity of metabolically active tissues (*23*,*24*,*28*). Further work is needed to elucidate these mechanisms.

Metabolic models of life history commonly assume continuity in cellular metabolism over the life course, with cellular metabolic rates increasing in a power-law manner (Energy = $a\text{Mass}^{b}$) and the energy available for growth during the juvenile period made available for reproduction in adults (*29,30*). DLW measures of humans here challenge this view, with FFM- and fat mass-adjusted metabolism elevated ~50% in childhood compared to adults (including pregnant females), and ~25% lower in the oldest subjects. It remains to be determined whether these fluctuations are common in other species. In addition to affecting energy balance, nutritional needs, and body weight, these metabolic changes present a potential target for clinical investigation into the kinetics of disease, pharmaceutical activity, and healing, processes intimately related to metabolic rate. Further, there is considerable metabolic variation among individuals, with TEE and its components varying more than ± 20% even when controlling for FFM, fat mass, sex, and age (Figure 1, 2, Table S2). With the pattern of metabolic activity over the lifespan established here, future work must investigate the processes underlying metabolic changes across the life course and variation among individuals, and the role of metabolic variation in health and disease.

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Conflict of interest

The authors have no conflicts of interest to declare.

Data Availability

All data used in these analyses is freely available via the IAEA Doubly Labelled Water Database (https://www.dlwdatabase.org/).

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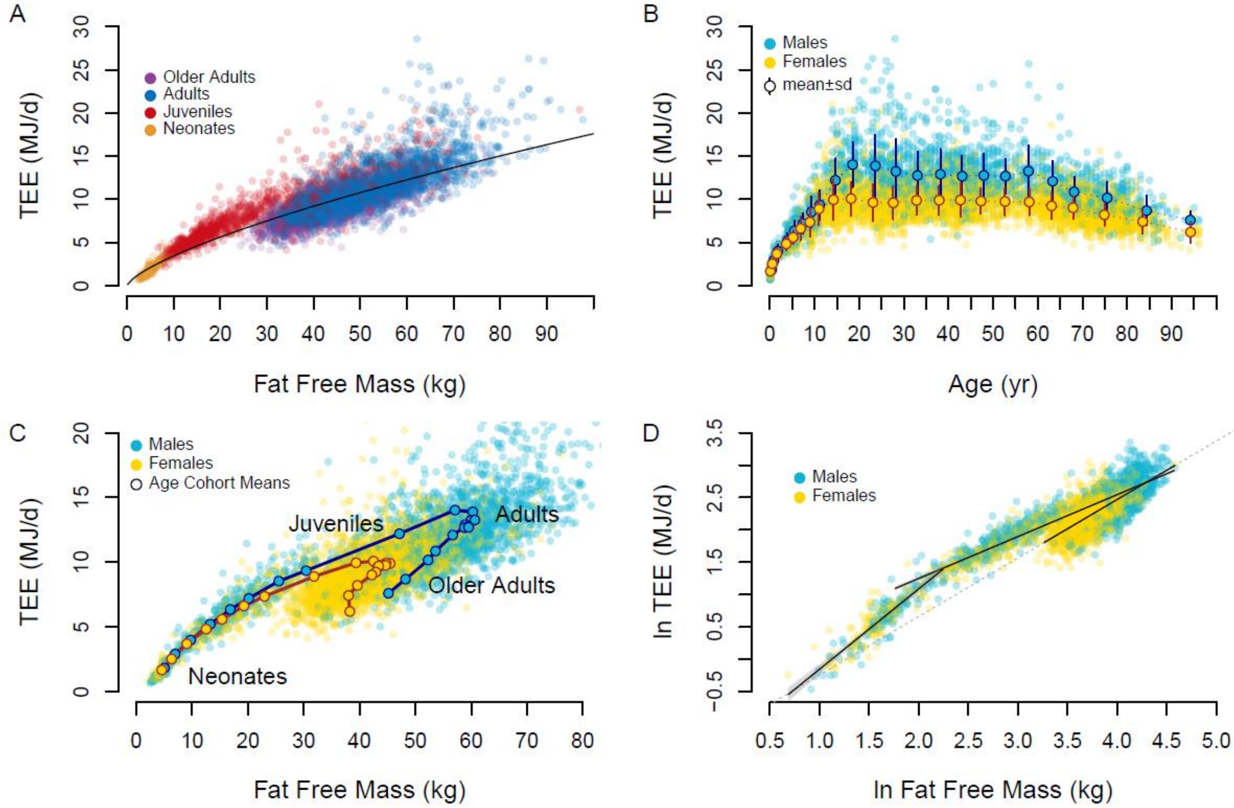

Figure 1. A. TEE increases with FFM in a power-law manner, but age groups cluster about the trend line differently. **B.** TEE rises in childhood, is stable through adulthood, and declines in older adults. Means±sd for age-sex cohorts are shown. **C.** Age-sex cohort means show a distinct progression of TEE and FFM over the life course. **D.** Neonate, juveniles, and adults exhibit distinct relationships between FFM and TEE. The dashed line, extrapolated from the regression for adults, approximates the regression used to calculate adjusted TEE values.

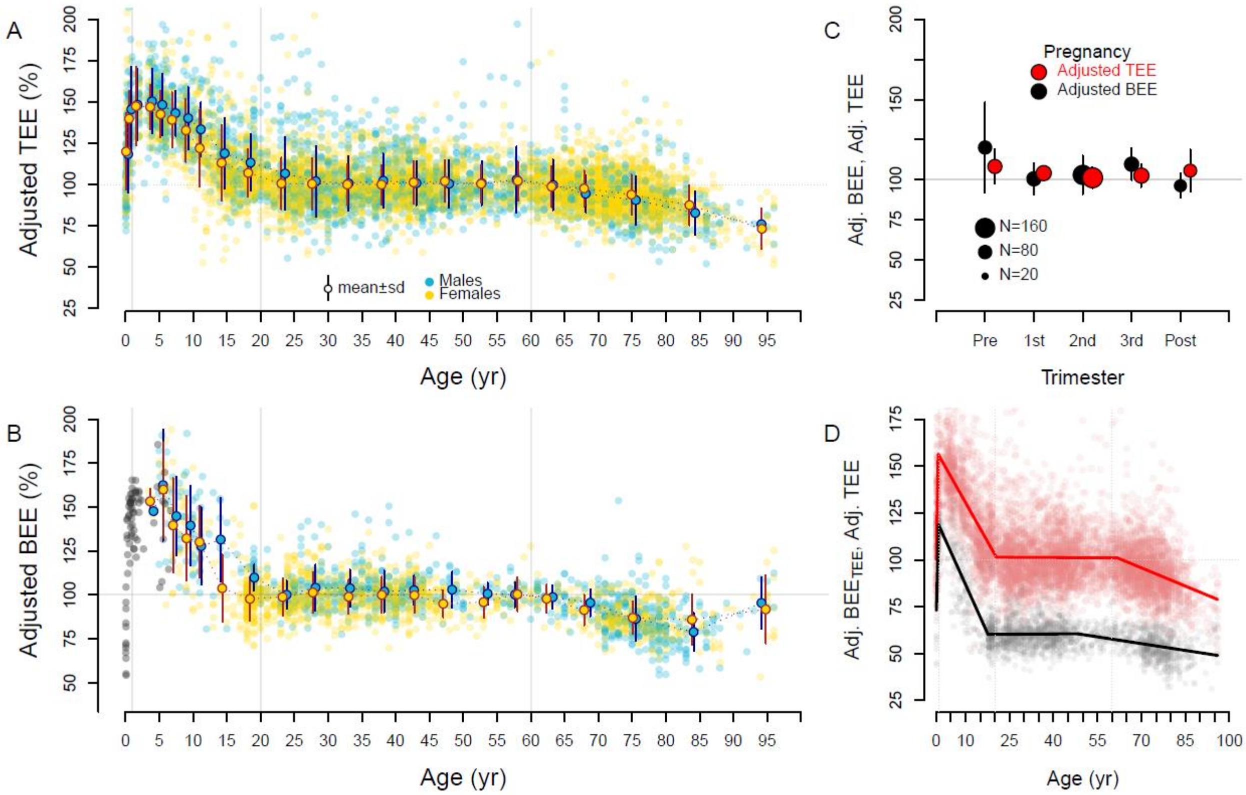

Figure 2. FFM and fat mass-adjusted expenditures over the life course. Individual subjects and age-sex cohort mean ± SD are shown. For both TEE (**A**) and BEE (**B**), adjusted expenditures begin near adult levels (~100%) but quickly climb to ~150% in the first year. Adjusted expenditures decline to adult levels ~20y, then decline again in older adults. BEE measures for infants and children not in the DLW database are shown in gray. **C.** Pregnant mothers exhibit adjusted TEE and BEE similar to non-reproducing adults. **D**. Segmented regression analysis of adjusted TEE (red) and adjusted BEE_{TEE} (black) indicates a peak at ~1 y, adult levels at ~20 y, and decline at ~60 y (see text).

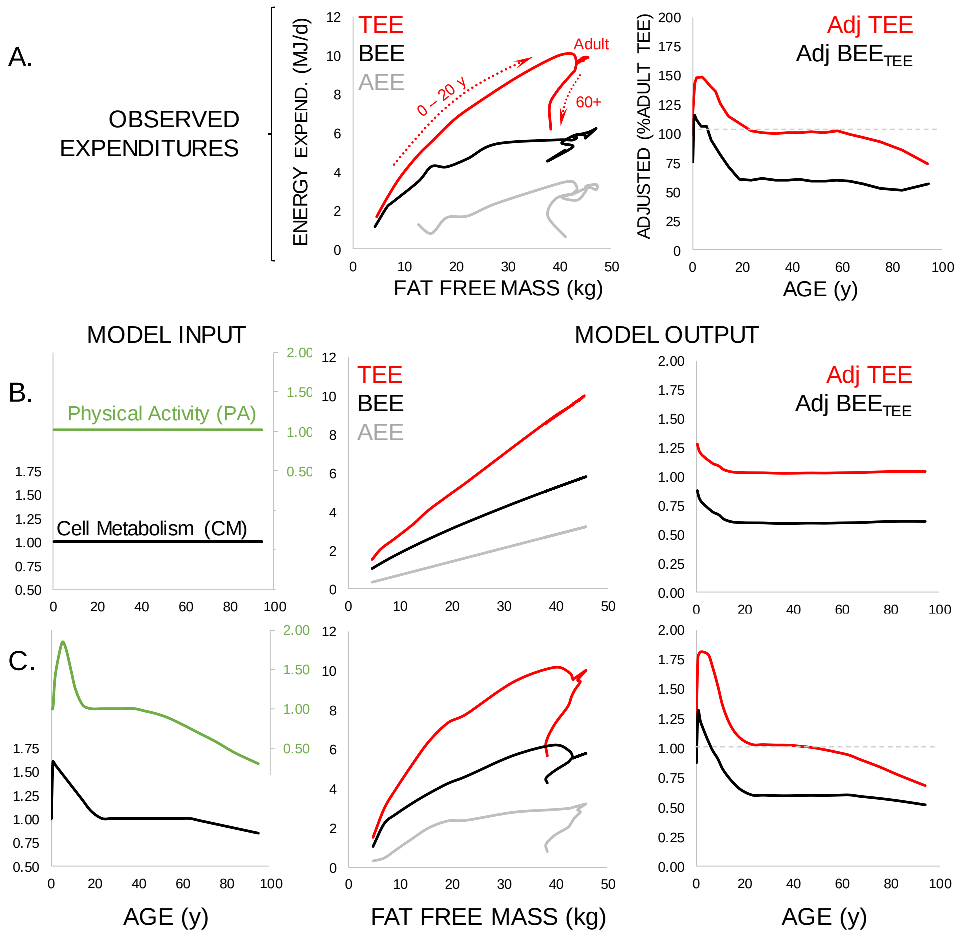

Figure 3. Modeling the contribution of PA and cellular metabolic activity (CM) to daily expenditures. **A.** Observed TEE, BEE, and AEE (Table S1) show age-related variation with respect to FFM (see Figure 1C) that is also evident in adjusted TEE and BEE_{TEE} (Table S3; see Figure 2D). **B.** These age effects do not emerge in models assuming constant PA and CM across the life course. **C.** When PA and CM follow the life course trajectories evident in accelerometer measured PA and adjusted BEE, respectively, model output is similar to observed expenditures.

Supplementary Materials:

Pontzer et al. *Daily Energy Expenditure through the Human Life Course*

Contents:

Material and Methods

1. <u>DLW Database</u>

Data were taken from IAEA Doubly Labelled Water (DLW) Database, version 3.1, completed April, 2020 (*19*). This version of the database comprises 6,743 measurements of TEE using the DLW method. Of these, a total of 6,421 had valid data for TEE, FFM, mass, sex, and age. These 6,421 measurements were used in this analysis. This dataset was augmented with published BEE measurements for n=136 neonates and infants (*31*-*36*) that included FFM and fat mass. Malnourished or preterm infants were excluded. For sources that provided cohort means rather than individual subject measurements (*33*,*36*) means were entered as single values into the dataset without reweighting to reflect sample size. This approach resulted in 77 measures of BEE, FFM, and fat mass for n=136 subjects. We also added to the dataset published BEE and TEE measurements of n=141 women before, during, and after pregnancy (*37-39*) that included FFM and fat mass. These measurements were grouped as pre-pregnancy, 1^{st} trimester, 2^{nd} trimester, 3^{rd} trimester, and post-partum for analysis.

In the DLW method (*8*), subjects were administered a precisely measured dose of water enriched in $^{2}H_2O$ and $H_2^{18}O$. The subject's body water pool is thus enriched in deuterium (^{2}H) and ^{18}O. The initial increase in body water enrichment from pre-dose values is used to calculate the size of the body water pool, measured as the dilution space for deuterium (N_d) and ^{18}O (N_o). These isotopes are then depleted from the body water pool over time: both isotopes are depleted *via* water loss, whereas ^{18}O is also lost *via* carbon dioxide production. Subtracting the rate (%/d) of deuterium depletion (k_d) from the rate of ^{18}O depletion (k_o), and multiplying the size of the body water pool (derived from N_d and N_o) provided the rate of carbon doxide production, rCO_2. Entries in the DLW database include the original k and N values for each subject, which were then used to calculate CO_2 using a common equation that has been validated in subjects across the lifespan (*40*). The rate of CO_2 production, along with each subject's reported food quotient, was then used to calculate energy expenditure (MJ/d) using the Weir equation (*41*).

The size of the body water pool, determined from N_d and N_o, was used to establish FFM, using hydration constants for FFM taken from empirical studies. Other anthropometric variables (age, height, body mass, sex) were measured using standard protocols. Fat mass was calculated as body mass – FFM.

2. BEE, AEE, and PAL

A total of 2,008 subjects in the database had associated BEE, measured *via* respirometry. For these subjects, we analyzed BEE, AEE, and PAL. AEE was calculated as (0.9TEE – BEE), which subtracts BEE and the assumed costs of digestion (0.1TEE) from TEE. The PAL ratio was calculated as TEE/BEE. As noted above, the BEE dataset was augmented with measurements from neonates and infants, but these additional measures do not have associated TEE and could not be used to calculate AEE or PAL.

3. Predictive Models for TEE, BEE, AEE, and PAL

We used general linear models to regress measures of energy expenditure against anthropometric variables. We used the base package in R version 3.4.4 (*43*) for all analyses. General linear models were implemented using the `lm` function. These models were used to develop predictive equations for TEE for clinical and research applications, and to determine the relative contribution of different variables to TEE and its components. Given the marked changes in metabolic rate over the lifespan (Figure 1, Figure 2) we calculated these models separately for each life history stage: infants (0 – 1 y), juveniles (1 – 20 y), adults (20 – 60 y), and older adults (60+ y). These age ranges were identified using segmented regression analysis. Results of these models are shown in Table S2.

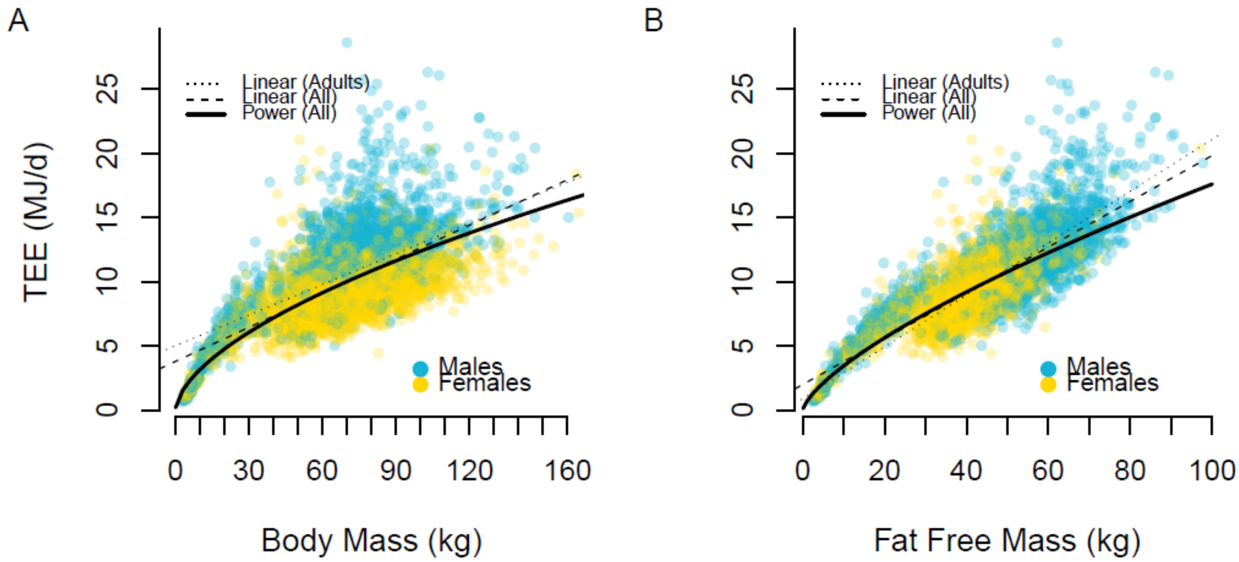

Figure S1. TEE increases with body size in a power-law manner. For the entire dataset (n = 6,407): **A.** the power-law regression for total body mass (*ln*TEE = 0.593 ± 0.004 *ln*Mass – 0.214 ± 0.018, $p < 0.001$, adj. $r^2 = 0.73$, model std. err. = 0.223, df = 6419) is less predictive than the regression for fat free mass (FFM, **B**) (*ln*TEE = 0.708 ± 0.004 *ln*FFM – 0.391 ± 0.015, $p < 0.001$, adj. $r^2 = 0.83$, model std. err. = 0.176, df = 6419). In body mass regressions (power and linear models), adult males cluster above the trend line while females cluster below due to sex differences in body composition. In contrast, males and females fit the FFM regression equally well. For both body mass and FFM regressions, power-law regressions outperform linear models, particularly at the smallest body sizes. For all models, for both body mass and FFM, children have elevated TEE, clustering above the trend line. Children also exhibit elevated BEE and AEE (Figure S2). Power-law regressions have an exponent < 1.0, and linear regressions (dashed: linear regression through all data; dotted: linear regression through adults only) have a positive intercept, indicating that simple ratios of (TEE/Body Mass) or (TEE/FFM) do not adequately control for differences in body size (*20*).

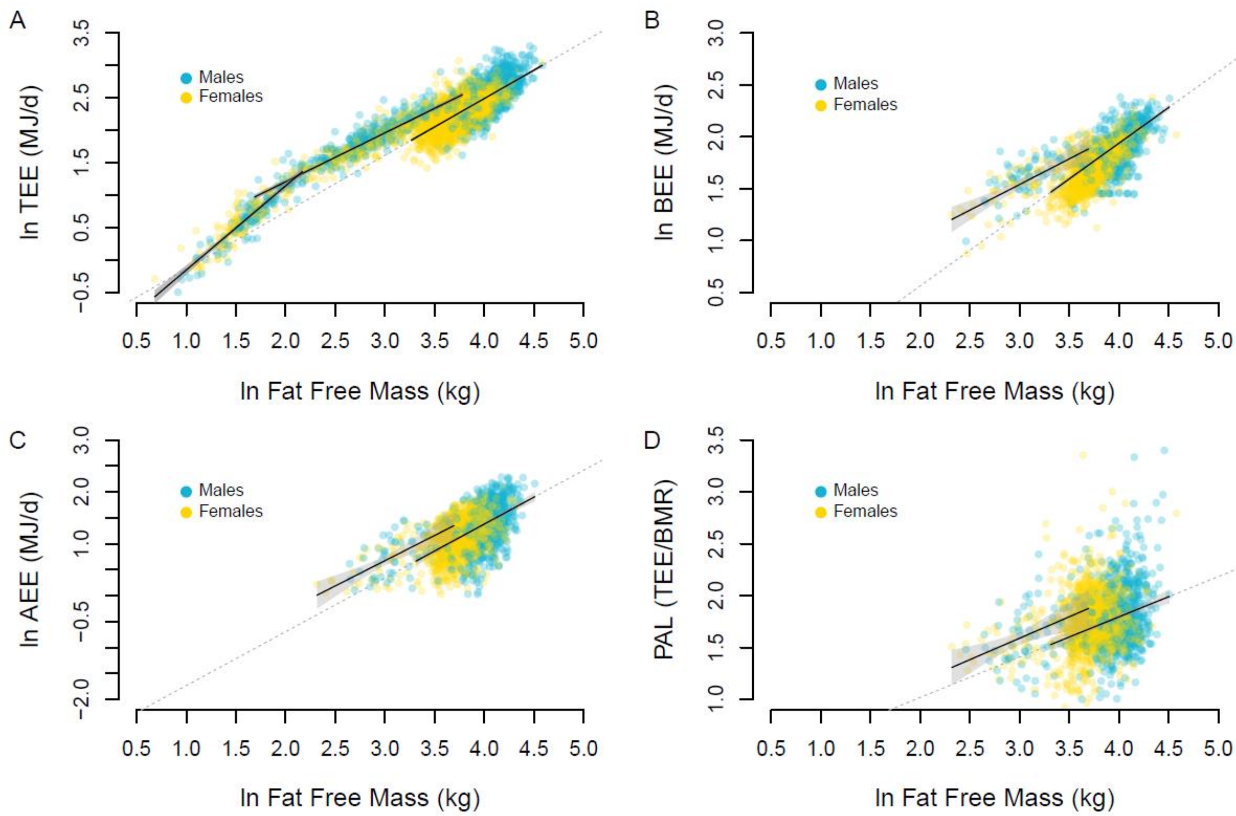

Figure S2. Infants and children exhibit different relationships between FFM and expenditure. PAL. **A:** For TEE, regressions for infants (left regression line) and adults (right regression line) intersect for neonates, at the smallest body size. However, the slopes differ, with the infants' regression and 95% CI (gray region) falling outside of that for adults (extrapolated dashed line). Children (middle regression line) are elevated, with a regression outside the 95% CI of adults. Children's regressions (with 95%CI) are also elevated for BEE (**B**), AEE (**C**), and PAL (**D**). Sex differences in expenditure (**A-D**) are attributable to differences in FFM.

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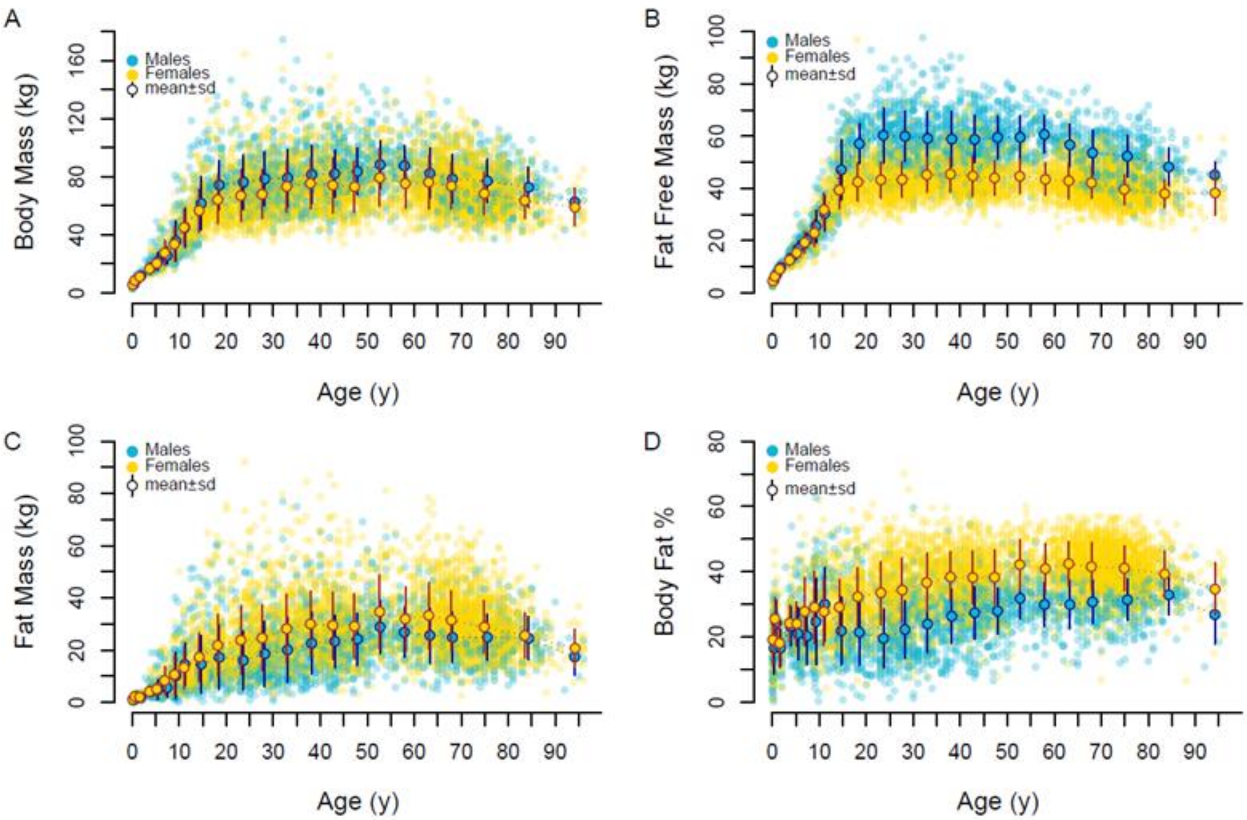


523 **Figure S3.** Changes in body composition over the lifespan: **A.** Body mass; **B.** Fat free mass (FFM); **C.**
524 Fat Mass; and **D.** Body fat percentage.

4. Adjusted TEE, Adjusted BEE, and Adjusted BEE_{TEE}

We used general linear models with FFM and fat mass in adults (25 – 60 y) to calculate adjusted TEE and adjusted BEE. We used models 2 and 5 in Table S2, which have the form *ln*(Expenditure)~*ln*(FFM) + *ln*(Fat Mass) and were implemented using the `lm` function in base R version 3.4.4 (R Core Team 2019). We used *ln*-transformed variables due to the inherent power-law relationship between body size and both TEE and BEE (ref. *2*; see Figure 1, Figure S1). Predicted values for each subject, given their FFM and fat mass, were calculated from the model using the `pred()` function; these *ln*-transformed values were converted back into MJ as exp(Predicted). Residuals for each subject were calculated as (Observed – Predicted) expenditure, and were then used to calculate adjusted expenditures as:

$$\text{Adjusted Expenditure} = 1 + \text{Residual} / \text{Predicted} \qquad [1]$$

The advantage of expressing residuals as a percentage of the predicted value is that it allows us to compare residuals across the range of age and body size in the dataset. Raw residuals (MJ) do not permit direct comparison because the relationship between size and expenditure is heteroscedastic; the magnitude of residuals increases with size (see Figure S1). Ln-transformed residuals (*ln*MJ) avoid this problem but are more difficult to interpret. Adjusted expenditures, used here, provide an easily interpretable measure of deviation from expected values. An adjusted expenditure value of 100% indicates that a subject's observed TEE or BEE matches the value predicted for their FFM and fat mass, based on the general linear model derived for adults. An adjusted expenditure of 120% indicates an observed TEE or BEE value that exceeds the predicted value for their FFM and fat mass by 20%. Similarly, an adjusted expenditure of 80% means the subject's measured expenditure was 20% lower than predicted for their FFM and fat mass using the adult model. Adjusted TEE and BEE values for each age-sex cohort are given in

Table S3. Within each metabolic life history stage we used general linear models (`lm` function in R) to investigate the effects of sex and age on adjusted TEE and BEE.

This same approach was used to calculate adjusted BEE as a proportion of TEE (Figure 2D), hereafter termed adjusted BEE_{TEE}. $Residual_{BEE\text{-}TEE}$, the deviation of observed BEE from the adult TEE regression (eq. 2 in Table S2), was calculated as (Observed BEE – Predicted TEE) and then used to calculate adjusted BEE_{TEE} as

$$\text{Adjusted } BEE_{TEE} = 1 + Residual_{BEE\text{-}TEE} / \text{Predicted TEE} \qquad [2]$$

When adjusted BEE_{TEE} = 80%, observed BEE is equal to 80% of predicted TEE given the subject's FFM and fat mass. Adjusted BEE_{TEE} is equivalent to adjusted BEE (Figure S4) but provides some analytical advantages. The derivation of adjusted BEE_{TEE} approach applies identical manipulations to observed TEE and observed BEE and therefore maintains them in directly comparable units. The ratio of adjusted TEE/adjusted BEE is identical to the PAL ratio of TEE/BEE, and the difference (0.9adjusted TEE – adjusted BEE) is proportional to AEE (Figure S4). Plotting adjusted TEE and adjusted BEE_{TEE} over the lifespan (Figure 2D) therefore shows both the relative magnitudes of TEE and BEE and their relationship to one another in comparable units.

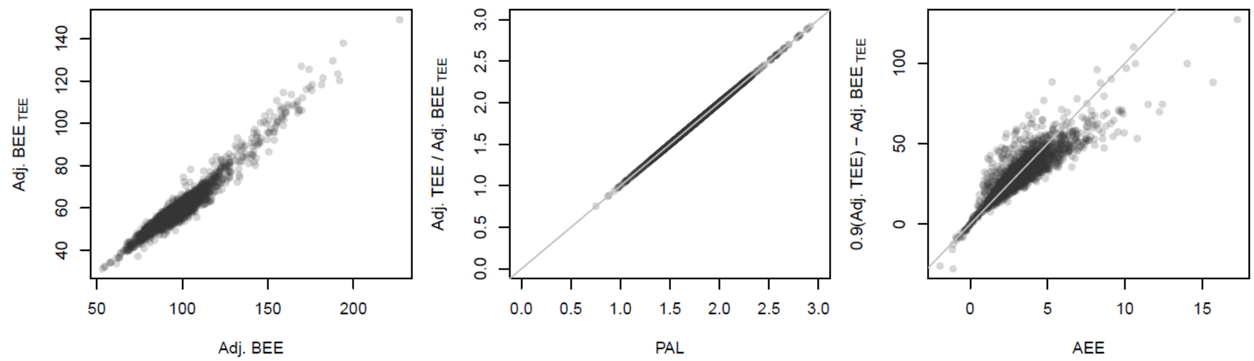
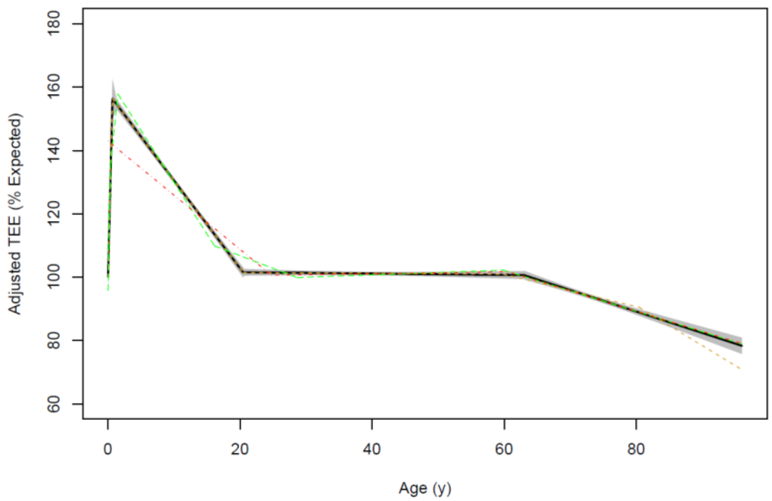


Figure S4. Left: Adjusted BEE$_{TEE}$ corresponds strongly to adjusted BEE. Center: The ratio of adjusted TEE/adjusted BEE$_{TEE}$ is identical to the PAL ratio (TEE/BMR). Right: The difference (0.9adjusted TEE – adjusted BEE$_{TEE}$) is proportional to AEE. Gray lines: center panel: y = x, right panel: y = 10x.

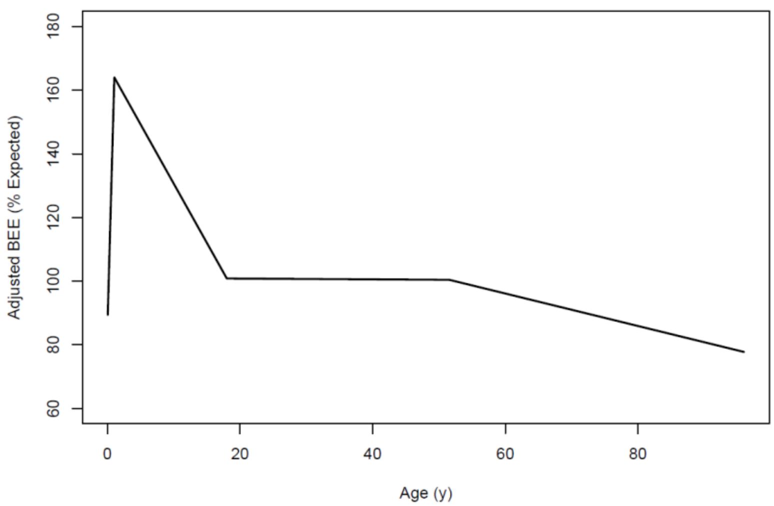
5. Segmented Regression Analysis

We used segmented regression analysis to determine the change points in the relationship between adjusted expenditure and age. We used the Segmented (version 1.1-0) package in R (*44*). For adjusted TEE, we examined a range of models with 0 to 5 change points, using the `npsi=` term in the `segmented()` function. This approach does not specify the location or value of change points, only the number of them. Each increase in the number of change points from 0 to 3 improved the model adj. R^2 and standard error considerably. Increasing the number of change points further to 4 or 5 did not improve the model, and the additional change points identifed by the `segmented()` function fell near the change points for the 3-change point model. We therefore selected the 3-change point model as the best fit for adjusted TEE in this dataset. Segmented regression results are shown in Table S4. A similar 3-change point segmented regression approach was conducted for adjusted BEE (Figure S4) and adjusted BEE$_{TEE}$ (Figure 2D). We note that the decline in adjusted BEE and adjusted BEE$_{TEE}$ in older adults begins earlier (as identified by segmented regression analysis) than does the decline in adjusted TEE among older adults. However, this difference may reflect the relative paucity of

BEE measurements for subjects 40 – 60 y. Additional measurements are needed to determine whether the decline in BEE does in fact begin earlier than the decline in TEE. Here, we view the timing as essentially coincident and interpret the change point in adjusted TEE (~60 y), which is determined with a greater number of measurements, as more accurate and reliable.



A.



B.

Figure S5. Segmented regression analysis of adjusted TEE (**A**) and adjusted BEE (**B**). In both panels, the black line and gray shaded confidence region depicts the 3 change-point regression. For adjusted TEE, segmented regressions are also shown for 2 change points (red), 4 change points (yellow), and 5 change points (green). Segmented regression statistics are given in Table S4.

6. Organ Size and BEE

Organs differ markedly in their mass-specific metabolic rates at rest (*45*). The heart (1848 kJ kg^{-1} d^{-1}), liver (840 kJ kg^{-1} d^{-1}), brain (1008 kJ kg^{-1} d^{-1}), and kidneys (1848 kJ kg^{-1} d^{-1}) have much greater mass-specific metabolic rates at rest than do muscle (55 kJ kg^{-1} d^{-1}), other lean tissue (50 kJ kg^{-1} d^{-1}), and fat (19 kJ kg^{-1} d^{-1}). Consequently, the heart, liver, brain, and kidneys combined account for ~60% of BEE in adults (*21*,*22*,*46*,*47*). In infants and children, these metabolically active organs constitute a larger proportion of body mass. The whole body mass-specific BEE (i.e., BEE/body mass, or BEE/FFM) for infants and children is therefore expected to be greater than adults' due to the greater proportion of metabolically active organs early in life (*22,46,47*). Similarly, reduced organ sizes in elderly subjects may result in declining BEE (*21*).

To examine this effect of organ size on BEE in our dataset, we used published references for organ size to determine the mass of the metabolically active organs (heart, liver, brain, and kidneys) as a percentage of body mass or FFM for subjects 0 – 12 y (*22*,*46-48*), 15 to 60 y (*21*,*22*), and 60 to 100 y (*21*,*49*). We used these relationships to estimate the combined mass of the metabolically active organs (heart, liver, brain, kidneys) for each subject in our dataset. We then subtracted the mass of the metabolically active organs from measured FFM to calculate the mass of "other FFM". These two measures, along with measured fat mass, provided a three-compartment model for each subject: metabolically active organs, other FFM, and fat (Figure S6A).

Following previous studies (*21-25*), we assigned mass-specific metabolic rates to each compartment and estimated BEE for each subject. We used reported mass-specific metabolic rates for the heart, liver, brain, and kidneys (see above; *45*) and age-related changes in the proportions of these organs for subjects 0 – 12 y (*22,48*), 15 to 60 y (*21-25*), and 60 to 100 y (*22-*

25,49) to calculate an age-based weighted mass-specific metabolic rate for the metabolically active organ compartment. We averaged the mass-specific metabolic rates of resting muscle and other lean tissue (see above; *21,22*) and assigned a value of 52.5 kJ kg^{-1} d^{-1} to "other FFM", and we used a mass-specific metabolic rate of 19 kJ kg^{-1} d^{-1} for fat.

Results are shown in Figure S6. Due to the greater proportion of metabolically active organs in early life, the estimated BEE from the three-compartment model follows a power-law relationship with FFM (using age cohort means, BEE= 0.38 $FFM^{0.75}$; Figure S6B) that is similar to that calculated from observed BEE in our dataset (see Table S2 and *Modeling the Effects of PA and Cellular Metabolism*, below). Estimated BEE from the three-compartment model produced mass-specific metabolic rates that are considerably higher for infants and children than for adults and roughly consistent with observed age-related changes in BEE/FFM (Figure S6C). Thus, changes in organ size can account for much of the variation in BEE across the lifespan observed in our dataset.

Nonetheless, observed BEE was ~30% greater early in life, and ~20% lower in older adults, than estimated BEE from the three-compartment model (Figure S6D). The departures from estimated BEE suggest that the mass-specific metabolic rates of one or more organ compartments are considerably higher early in life, and lower late in life, than they are in middle-aged adults, consistent with previous assessments (*21-25*). It is notable, in this context, that observed BEE for neonates is nearly identical to BEE estimated from the three-comparment model, which assumes adult-like tissue metabolic rates (Figure S6B,C,D). Observed BEE for neonates is thus consistent with the hypothesis that the mass-specific metabolic rates of their organs are similar to those of other adults, specifically the mother.

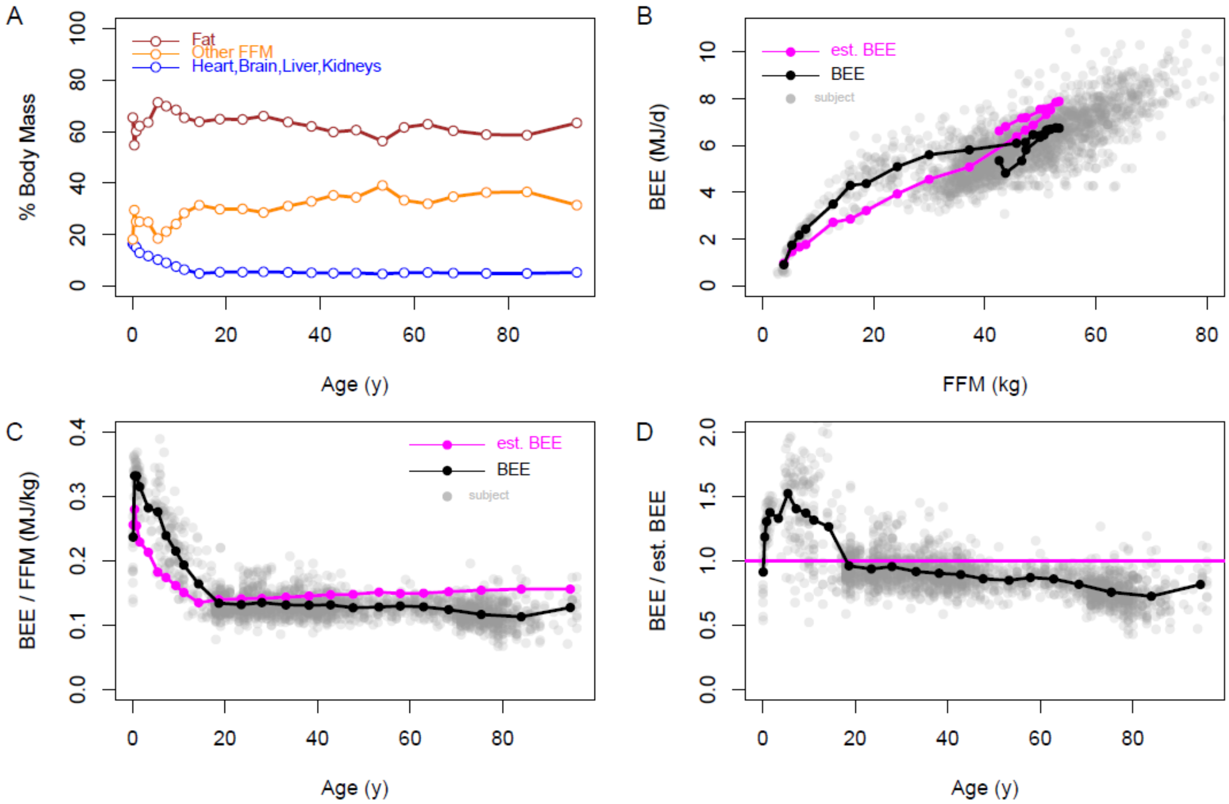


Figure S6. Organ sizes and BEE. A. The relative proportions of metabolically active organs (heart, brain, liver, kidneys), other FFM, and fat changes over the life course. Age cohort means are shown. **B.** Consequently, estimated BEE from the three-compartment model increases with FFM in a manner similar to observed BEE, with **C.** greater whole body mass-specific BEE early in life. **D.** Observed BEE is ~30% greater early in life, and ~20% lower after age 60 y, than estimated BEE from the three-compartment model. In panels **B**, **C**, and **D**, age-cohort means for observed BEE (black) and estimated BEE (magenta) are shown.

7. <u>Modeling the Effects of PA and Cellular Metabolism</u>

We constructed two simple models to examine the contributions of PA and variation in cellular metabolic rate to TEE, BEE and AEE. In the simplest version, we used the observed relationship between BEE and FFM for all adults 20 – 60 y determined from linear regression of *ln*BEE and *ln*FFM (untransformed regression equation: BEE = 0.32 $FFM^{0.75}$, adj. $r^2 = 0.60$, df = 1684, $p < 0.0001$) to model BEE as

$$BEE = 0.32\ CM_{age}\ FFM^{0.75} \qquad [3]$$

The CM_{age} term is cellular metabolic rate, a multiplier between 0 and 2 reflecting a relative increase ($CM_{age} > 1.0$) or decrease ($CM_{age} < 1.0$) in cellular activity relative that expected from the power-law regression for adults. Note that, even when $CM_{age} = 1.0$, smaller individuals are expected to exhibit greater mass-specific BEE (that is, a greater BEE kg^{-1}) due to the power-law relationship between BEE and FFM. Further, we note that the power-law relationship between BEE and FFM for adults is similar to that produced when estimating BEE from organ sizes (see *Organ Size and BEE*, above). Thus, variation in CM_{age} reflects modeled changes in cellular metabolic rate *in addition* to power-law scaling effects, and also, in effect, in addition to changes in BEE due to age-related changes in organ size. To model variation in cellular activity over the lifespan, we either 1) maintained CM_{age} at adult levels ($CM_{age} = 1.0$) over the entire lifespan, or 2) had CM_{age} follow the trajectory of adjusted BEE with age (Figure S8).

To incorporate effects of fat mass into the model, we constructed a second version of the model in which BEE was modeled following the observed relationship with FFM and fat mass for adults 20 – 60 y,

$$BEE = 0.32\ CM_{age}\ FFM^{0.7544}\ FatMass^{0.0003} \qquad [4]$$

As with the FFM model, we either maintained CM_{age} at 1.0 over the life span or modeled it using the trajectory of adjusted BEE.

AEE was modeled as a function of PA and body mass assuming larger indivduals expend more energy during activity. The observed ratio of AEE/FFM for adults 20 – 60 y was 0.07 MJ d^{-1} kg^{-1}. We therefore modeled AEE as

$$AEE = 0.07\ PA_{age}\ FFM \qquad [5]$$

To incorporate effects of fat mass, we constructed a second version using the ratio of AEE/(FFM+FatMass) for adults 20 – 60y,

$$AEE = 0.04\ PA_{age}\ (FFM + Fat\ Mass) \qquad [6]$$

In both equations, PA_{age} represents the level of physical activity relative to the mean value for 20 – 60 y adults. PA_{age} could either remain constant at adult levels (PA_{age}=1.0) over the lifespan or follow the trajectory of PA measured *via* accelerometry, which peaks between 5 – 10 y, declines rapidly through adolescence, and then declines more slowly beginning at ~40 y (*15-17*,*26*,*27*, *50-52*). Different measures of PA (*e.g.*, moderate and vigorous PA, mean counts per min., total accelerometry counts) exhibit somewhat different trajectories over the lifespan, but the patterns are strongly correlated; all measures show the greatest activity at 5-10 y and declining activity in older adults (Figure S7). We chose total accelerometry counts (*15*,*27*), which sum all movement per 24-hour period, to model age-related changes in PA_{age}.

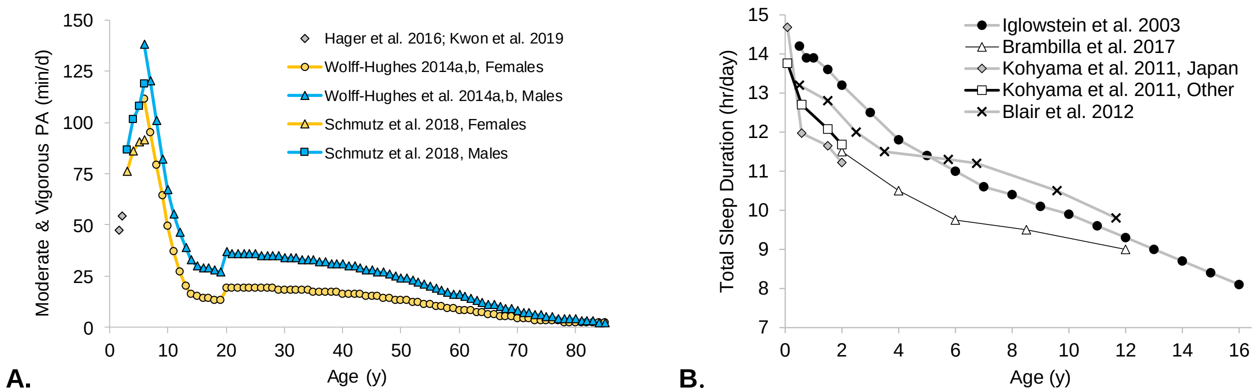


Figure S7. Modeling PA across the lifespan. **A.** Across studies and countries, accelerometer-measured PA rises through infancy and early childhood, peaking between 5 and 10y before declining to adult levels in the teenage years (*15-17,26,27, 50-54*). PA declines again, more slowly, in older adults. The onset of decline in older adults varies somewhat across studies, beginning between ~40 y and ~60 y. Here, PA is shown as minutes/day of moderate and vigorous PA. Other measures of PA (*e.g.*, total accelerometer counts; mean counts/min, vector magnitude) follow a similar pattern of PA over the life span (*15, 27*). **B.** The increase in PA from 0 to ~10 y is mirrored by the steady decline in total daily sleep duration during this period (*55-58*).

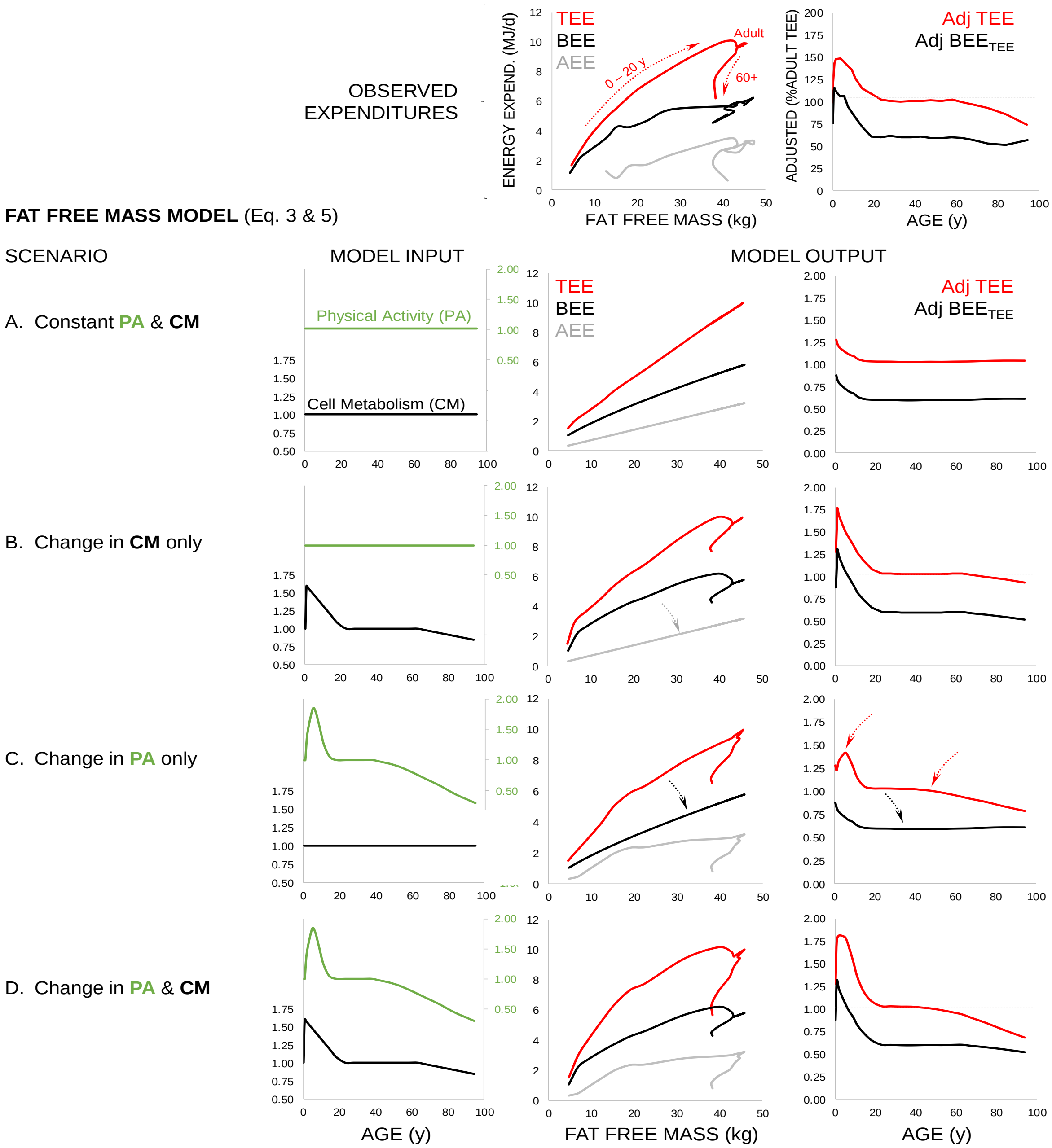


Figure S8. Results of the FFM model. Observed expenditures exhibit a marked age effect on the relationship between expenditure and FFM that is evident in both absolute (Figure 1C) and adjusted (Figure 2D) measures. **A.** If physical activity (PA) and cellular metabolism (CM) remain constant at adult levels, age effects do not emerge from the model. **B.** When only CM varies, age effects emerge for TEE and BEE, but not AEE (gray arrow). **C.** Conversely, if only PA varies age emerge for AEE and TEE but not BEE (black arrows). Adjusted TEE also peaks later in childhood and declines earlier in adulthood (red arrows) than observed. **D.** Varying both PA and CM gives model outputs similar to observed expenditures.

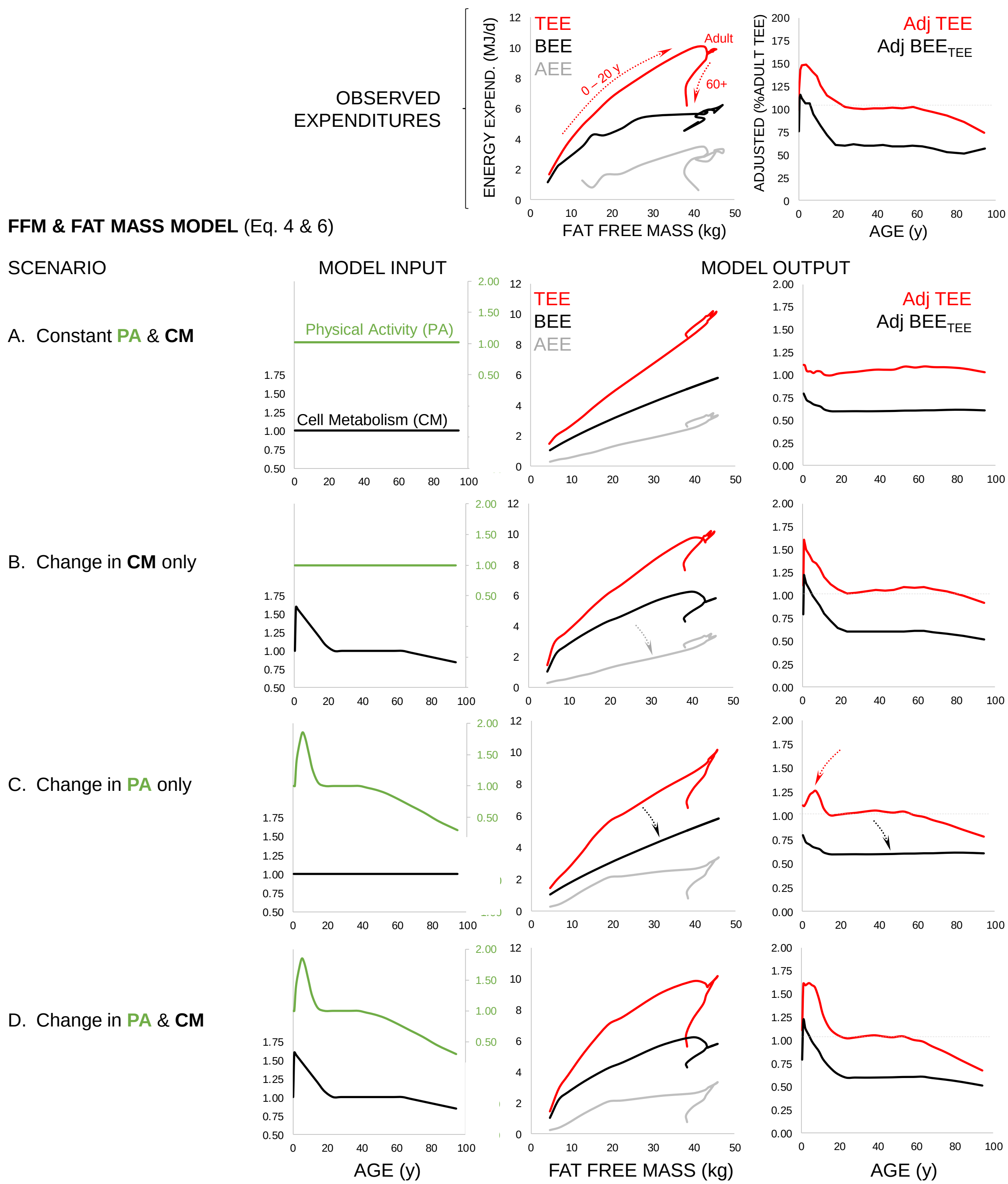


Figure S9. Results of the FFM and Fat Mass model. Model outputs are similar to those of the FFM model (Figure 7). The scenario that best matches the observed relationships between FFM, age, and expenditure is E, in which AEE is influenced by age-related variation in both PA and cellular metabolism.

Table S1. Key characteristics by age-se cohort for A. TEE from the DLW database and B. subjects with BEE measurements. *Infant data from the literature, males and females pooled. N values for infant BEE (0 to 2 years) indicate number of entries and (number of individuals). See Methods.

A.

Age group	F N	M N	Age F mean sd	Age M mean sd	Height F mean sd	Height M mean sd	Mass F mean sd	Mass M mean sd	BMI F mean sd	BMI M mean sd	FFM F mean sd	FFM M mean sd	FM F mean sd	FM M mean sd	Fat% F mean sd	Fat% M mean sd	TEE F mean sd	TEE M mean sd
(0,0.5]	102	93	0.24 0.13	0.24 0.13	59.7 4.6	60.4 5.4	5.71 1.28	6.12 1.52	15.8 1.6	16.4 1.9	4.56 0.87	5.03 1.09	1.14 0.63	1.09 0.66	19.2 7.7	16.6 7.8	1.68 0.46	1.83 0.58
(0.5,1]	18	23	0.68 0.18	0.72 0.20	69.1 4.3	71.8 4.6	8.54 1.40	9.17 1.33	17.8 2.1	17.7 1.3	6.32 0.91	6.94 1.18	2.23 0.80	2.23 0.65	25.6 6.4	24.3 6.7	2.53 0.36	2.90 0.78
(1,2]	33	35	1.70 0.46	1.64 0.48	82.3 5.0	83.2 5.9	11.06 1.41	11.69 1.65	16.3 1.0	16.8 1.0	9.04 1.32	9.74 1.41	2.02 0.87	1.96 0.76	18.1 7.5	16.7 5.7	3.70 0.64	3.99 0.74
(2,4]	54	48	3.81 0.28	3.78 0.31	101.2 4.6	102.1 6.1	16.66 3.38	17.38 3.03	15.9 1.7	16.6 2.4	12.51 1.85	13.24 1.85	4.15 1.91	4.14 1.69	24.2 5.5	23.2 5.8	4.84 0.70	5.21 0.89
(4,6]	99	121	5.34 0.63	5.31 0.68	112.7 6.7	113.7 7.5	20.41 3.86	21.74 5.73	16.0 2.0	16.6 2.9	15.34 2.31	16.83 2.92	5.06 2.43	4.91 3.55	24.1 6.8	21.1 8.0	5.59 0.80	6.35 1.18
(6,8]	42	43	7.03 0.65	7.25 0.62	122.5 10.2	125.2 8.8	27.62 8.49	25.71 5.49	18.0 3.9	16.2 2.4	19.28 3.97	20.14 2.75	8.34 5.33	5.57 3.62	27.8 10.3	20.3 8.7	6.62 1.36	7.20 1.13
(8,10]	79	75	9.10 0.48	9.14 0.53	133.5 9.3	136.9 10.0	33.62 11.50	35.76 13.69	18.2 4.5	18.4 4.8	22.96 5.01	25.53 6.09	10.66 7.74	10.23 8.76	29.1 10.9	24.7 13.1	7.36 1.67	8.54 1.77
(10,12]	69	34	11.14 0.58	11.01 0.47	148.5 8.0	143.7 9.6	45.15 11.65	44.91 13.45	20.3 4.1	21.2 4.4	31.85 6.35	30.42 6.63	13.30 7.90	14.50 8.25	27.8 10.3	30.1 11.2	8.90 1.88	9.35 1.68
(12,16]	227	129	14.37 1.18	14.53 1.14	160.6 8.4	168.4 12.1	56.72 14.67	61.73 18.36	21.9 4.8	21.5 5.6	39.37 7.27	47.15 11.42	17.34 9.25	14.58 10.95	29.2 8.3	21.9 10.4	9.96 2.35	12.20 2.53
(16,20]	211	103	18.32 0.99	18.37 1.11	163.9 7.4	177.9 7.7	64.31 16.34	74.36 16.73	23.9 5.8	23.5 4.9	42.49 7.26	57.11 7.58	21.82 11.76	17.25 12.26	32.3 8.9	21.5 10.0	10.08 1.95	14.02 2.59
(20,25]	257	128	23.23 1.40	23.48 1.38	164.6 7.4	177.6 9.3	67.08 17.92	76.35 18.60	24.8 6.4	24.1 4.9	43.26 6.97	60.29 10.53	23.82 13.08	16.06 11.14	33.6 9.6	19.6 8.9	9.64 2.12	13.88 3.56
(25,30]	281	186	27.77 1.48	28.05 1.40	164.1 6.9	177.4 8.9	67.99 16.72	78.56 18.51	25.2 5.9	24.9 4.8	43.36 6.81	59.97 9.63	24.63 12.51	18.58 12.54	34.4 9.8	22.3 8.6	9.60 1.94	13.24 3.75
(30,35]	238	149	32.99 1.36	32.88 1.41	164.5 6.2	177.2 8.0	73.39 17.78	79.14 19.56	27.2 6.3	25.1 5.4	45.20 6.63	59.07 10.23	28.18 12.96	20.07 12.18	36.7 9.0	24.0 8.7	9.88 1.65	12.76 2.79
(35,40]	232	167	38.05 1.45	38.01 1.42	164.2 6.5	176.7 7.6	75.50 17.68	81.55 19.88	28.0 6.6	26.0 5.4	45.47 6.82	58.91 10.51	30.03 12.59	22.64 11.78	38.4 7.7	26.4 8.3	9.90 1.68	12.90 2.92
(40,45]	301	165	42.81 1.36	42.92 1.37	163.7 7.2	176.3 7.7	74.23 18.78	82.12 15.90	27.6 6.3	26.4 4.3	44.76 7.56	58.79 8.91	29.47 12.78	23.33 9.98	38.2 8.0	27.4 7.9	9.92 1.94	12.68 2.39
(45,50]	172	144	47.43 1.46	47.76 1.46	164.6 6.1	176.8 7.2	73.18 17.40	83.74 15.81	27.4 6.3	27.2 4.3	44.02 6.44	59.52 8.15	29.15 12.40	24.21 9.91	38.3 8.3	28.0 7.1	9.80 1.48	12.77 2.47
(50,55]	105	93	52.80 1.48	52.59 1.48	163.5 5.9	177.1 6.7	79.37 19.42	88.38 16.51	29.7 7.0	28.4 4.8	44.66 6.51	59.54 8.29	34.72 14.08	28.84 10.08	42.2 7.8	31.8 6.1	9.75 1.59	12.69 2.03
(55,60]	111	76	58.24 1.48	57.76 1.38	163.6 6.2	177.3 7.6	75.35 17.07	87.53 13.91	28.3 5.7	27.8 3.7	43.42 6.06	60.67 7.13	31.93 12.22	26.86 9.42	41.0 7.7	30.0 6.7	9.70 1.54	13.27 2.97
(60,65]	252	90	63.22 1.47	63.16 1.55	161.5 7.1	174.5 7.4	76.21 18.34	82.34 17.11	29.3 6.8	27.2 4.5	42.92 6.83	56.70 8.07	33.29 12.58	25.64 10.52	42.5 6.7	29.9 7.4	9.24 1.54	12.09 2.36
(65,70]	387	90	68.04 1.47	67.98 1.37	161.4 6.7	172.4 7.3	73.67 15.55	78.50 16.64	28.3 5.7	26.2 4.5	42.20 5.85	53.61 8.62	31.47 11.13	24.89 9.55	41.6 7.2	30.8 6.4	9.02 1.32	10.86 1.79
(70,80]	682	232	75.05 2.79	75.40 2.92	159.4 6.7	171.3 8.0	68.50 14.42	77.19 14.92	26.9 5.2	26.2 4.2	39.62 5.65	52.29 7.86	28.88 10.12	24.90 8.74	41.1 6.7	31.4 6.3	8.21 1.30	10.17 1.80
(80,90]	149	66	83.65 2.40	84.20 2.50	157.5 7.2	168.7 7.5	63.61 12.29	72.76 13.80	25.7 4.7	25.5 4.2	38.02 5.22	48.22 7.07	25.59 8.70	24.53 8.24	39.3 7.0	32.9 6.2	7.43 1.36	8.69 1.70
(90,100]	22	8	94.36 1.79	94.00 1.85	158.0 9.1	168.8 3.0	58.98 12.81	62.60 9.47	23.6 4.1	22.0 3.4	38.26 8.50	45.18 4.93	20.72 7.23	17.42 6.93	34.7 7.9	26.9 8.9	6.20 1.20	7.60 1.03

B.

Age Group	F N	M N	Age F mean sd	Age M mean sd	Mass F mean sd	Mass M mean sd	FFM F mean sd	FFM M mean sd	FM F mean sd	FM M mean sd	Fat% F mean sd	Fat% M mean sd	BEE F mean sd	BEE M mean sd	AEE F mean sd	AEE M mean sd	PAL F mean sd	PAL M mean sd
*(0,0.5]**	*22 (111)*		*0.21 0.17*		*5.45 1.6*		*4.17 0.81*		*1.3 0.80*		*21.21 8.94*		*1.14 0.52*					
*(0.5,1]**	*20 (88)*		*0.85 0.14*		*8.76 1.12*		*6.55 0.70*		*2.2 0.53*		*24.97 3.76*		*2.17 0.29*					
*(1,2]**	*18 (86)*		*1.56 0.32*		*10.33 1.73*		*7.72 1.12*		*2.6 0.69*		*24.96 3.27*		*2.44 0.44*					
(2,4]	3	1	3.80 0.35	4.00 NA	21.6 8.3	18.0 NA	14.87 4.25	14.96 NA	6.7 4.0	3.0 NA	29.54 6.26	16.91 NA	4.07 0.67	3.93 NA	1.27 0.45	1.37 NA	1.45 0.09	1.50 NA
(4,6]	9	11	5.74 0.34	5.41 0.47	19.1 2.9	19.9 3.7	15.16 2.78	16.81 2.61	3.9 1.8	3.1 1.5	20.41 8.91	15.04 4.77	4.26 0.82	4.69 1.05	0.81 0.84	1.16 0.60	1.34 0.21	1.41 0.20
(6,8]	18	13	7.19 0.58	7.38 0.72	24.5 6.5	24.7 4.6	18.07 3.75	20.01 2.50	6.4 4.4	4.6 3.8	24.29 11.13	17.41 10.59	4.24 0.85	4.71 0.59	1.62 0.78	2.04 1.22	1.54 0.19	1.61 0.30
(8,10]	22	21	9.19 0.64	9.49 0.61	31.6 13.0	35.6 12.9	22.19 4.08	26.32 6.07	9.4 10.4	9.2 7.8	25.80 13.92	22.26 13.20	4.67 0.87	5.53 0.95	1.72 1.02	2.74 1.25	1.54 0.26	1.68 0.27
(10,12]	5	18	11.12 0.61	11.07 0.28	36.2 6.3	45.3 13.9	27.77 3.42	30.56 6.44	8.4 4.4	14.7 8.5	22.44 8.25	29.96 10.88	5.43 0.87	5.66 0.65	2.38 0.71	2.74 1.24	1.62 0.21	1.66 0.28
(12,16]	18	11	14.47 1.33	13.95 0.87	65.8 26.5	44.0 14.0	40.05 11.53	32.51 7.19	25.7 16.8	11.5 7.5	35.77 12.72	24.17 8.02	5.65 1.18	6.10 1.08	3.43 1.83	2.34 1.51	1.80 0.34	1.55 0.32
(16,20]	154	41	18.57 0.83	18.92 0.75	63.7 15.9	74.8 12.5	42.43 7.32	57.96 7.28	21.3 11.2	16.8 9.2	31.95 8.30	21.65 8.25	5.63 0.95	7.86 0.90	3.51 1.26	5.74 1.59	1.82 0.25	1.93 0.24
(20,25]	135	42	23.41 1.40	23.70 1.37	66.4 19.2	77.5 19.3	43.32 7.03	60.09 11.38	23.1 13.7	17.4 11.0	32.62 9.55	21.25 8.61	5.77 0.81	7.34 1.24	3.12 1.75	4.99 2.39	1.71 0.32	1.86 0.32
(25,30]	114	71	27.90 1.46	27.98 1.44	65.9 17.4	75.5 20.9	42.37 7.04	58.82 9.21	23.5 12.9	16.7 15.1	33.50 10.86	20.50 8.21	5.83 0.87	7.50 1.17	2.85 1.58	4.62 2.92	1.65 0.27	1.80 0.39
(30,35]	95	71	33.18 1.34	33.10 1.47	74.8 20.3	77.5 18.3	45.46 6.95	58.52 9.23	29.3 14.6	18.9 11.8	36.97 9.70	23.09 8.65	6.03 0.94	7.47 1.09	3.20 1.17	4.40 2.21	1.71 0.22	1.77 0.31
(35,40]	112	87	38.10 1.41	38.17 1.45	78.5 20.6	80.1 20.2	46.96 7.57	58.10 9.93	31.5 14.9	22.0 12.3	38.29 9.00	25.86 8.49	6.22 0.83	7.32 1.17	3.09 1.25	4.40 1.79	1.67 0.23	1.78 0.26
(40,45]	99	53	42.92 1.33	42.57 1.29	80.8 22.2	82.3 18.5	47.08 8.20	59.28 9.50	33.8 15.3	23.0 12.5	39.94 8.82	26.35 9.81	6.24 1.02	7.50 1.09	3.35 1.32	4.46 2.03	1.72 0.24	1.77 0.28
(45,50]	37	30	47.19 1.27	48.20 1.37	75.5 20.7	92.9 18.6	45.01 7.42	63.72 6.48	30.5 14.5	29.1 13.7	38.08 10.35	29.89 8.78	5.73 0.78	7.99 1.16	3.27 0.79	5.06 1.99	1.75 0.17	1.83 0.30
(50,55]	32	13	53.16 1.57	53.46 1.20	80.5 20.7	92.2 19.6	45.18 5.96	61.65 7.44	35.3 15.7	30.6 13.5	41.92 8.73	31.98 7.19	5.84 0.81	7.64 0.96	3.11 0.91	4.49 1.39	1.71 0.16	1.77 0.20
(55,60]	22	23	58.18 1.40	57.52 1.24	71.0 12.6	87.0 10.2	43.40 4.84	61.72 6.29	27.6 8.9	25.3 7.2	38.09 5.81	28.68 5.83	5.92 0.83	7.56 0.72	2.55 0.76	4.35 1.50	1.60 0.15	1.75 0.22
(60,65]	22	37	62.50 1.44	63.11 1.66	65.7 10.1	79.9 12.6	40.40 5.51	56.76 5.89	25.3 5.9	23.2 8.2	38.16 4.80	28.22 6.25	5.49 0.82	7.02 0.79	2.68 0.79	4.16 1.43	1.68 0.23	1.78 0.28
(65,70]	40	29	68.05 1.64	68.66 1.45	71.2 16.3	76.4 15.1	42.61 5.96	53.98 9.37	28.6 11.7	22.4 7.3	38.96 7.67	28.78 5.58	5.30 0.61	6.53 0.93	2.87 0.88	3.37 1.21	1.72 0.20	1.70 0.24
(70,80]	187	192	75.25 2.87	75.42 2.96	67.1 14.6	80.2 14.0	39.22 6.23	53.83 7.24	27.9 10.0	26.3 8.6	40.59 6.78	32.14 6.27	4.76 0.71	5.91 1.00	2.62 1.14	3.30 1.37	1.73 0.28	1.75 0.30
(80,90]	46	46	84.02 2.58	83.96 2.31	63.3 12.9	75.6 14.3	37.66 5.74	49.76 7.38	25.7 8.9	25.9 8.2	39.58 7.41	33.49 5.41	4.55 0.81	5.10 0.85	1.72 0.93	2.88 1.26	1.56 0.27	1.75 0.31
(90,100]	14	8	94.93 1.44	94.00 1.85	62.4 12.2	62.6 9.5	41.07 8.83	45.18 4.93	21.4 7.0	17.4 6.9	33.97 8.06	26.90 8.93	5.11 1.05	5.79 1.28	0.63 1.17	1.05 1.02	1.29 0.32	1.35 0.22

Table S2. Model parameters for TEE, BMR, AEE, and PAL ($p<0.0001$ for all models)

TEE

Model	Factors	Neonates (0 - 1y)				Juveniles (1 - 20y)				Adults (20 - 60y)				Older Adults (60+ y)			
		β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p
1. TEE~Body Mass+Sex+Age	Intercept	0.255	0.111	2.304	0.022	2.592	0.118	22.032	0.000	5.984	0.197	30.427	0.000	10.917	0.375	29.130	0.000
	Body Mass	0.205	0.025	8.061	0.000	0.080	0.004	22.494	0.000	0.065	0.002	30.274	0.000	0.048	0.002	24.701	0.000
	Sex(M)	0.090	0.046	1.953	0.052	1.436	0.095	15.145	0.000	2.669	0.081	33.036	0.000	1.659	0.070	23.672	0.000
	Age	0.951	0.205	4.632	0.000	0.183	0.015	11.832	0.000	-0.025	0.004	-6.635	0.000	-0.080	0.004	-18.451	0.000
	model	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*
		235	0.343	231	0.733	1403	1.719	1399	0.726	2805	2.032	2801	0.482	1978	1.311	1974	0.509
		β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p
2. ln(TEE)~ln(FFM)+ln(FM)	Intercept	-1.270	0.074	-17.130	0.000	-0.121	0.028	-4.259	0.000	-1.102	0.050	-22.038	0.000	-0.773	0.062	-12.403	0.000
	ln FFM	1.163	0.046	25.311	0.000	0.696	0.011	60.758	0.000	0.916	0.013	71.248	0.000	0.797	0.018	44.723	0.000
	ln FM	0.053	0.014	3.862	0.000	-0.041	0.007	-5.714	0.000	-0.030	0.005	-5.986	0.000	-0.016	0.009	-1.828	0.068
	model	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*
		235	0.160	232	0.796	1403	0.154	1400	0.842	2805	0.142	2802	0.646	1978	0.139	1975	0.533
		β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p
3. ln(TEE)~ln(FFM)+ln(FM)+Sex+Ag	Intercept	-1.122	0.089	-12.619	0.000	-0.348	0.044	-7.956	0.000	-1.118	0.069	-16.129	0.000	0.092	0.089	1.032	0.302
	ln FFM	1.025	0.067	15.215	0.000	0.784	0.021	38.119	0.000	0.920	0.020	45.942	0.000	0.736	0.025	29.883	0.000
	ln FM	0.034	0.015	2.294	0.023	-0.019	0.007	-2.622	0.009	-0.032	0.006	-5.149	0.000	-0.030	0.010	-3.118	0.002
	Sex(M)	-0.014	0.021	-0.644	0.520	0.067	0.009	7.592	0.000	-0.002	0.009	-0.249	0.803	0.011	0.010	1.042	0.298
	Age	0.254	0.082	3.104	0.002	-0.012	0.002	-6.630	0.000	0.000	0.000	0.765	0.444	-0.008	0.000	-19.038	0.000
	model	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*
		235	0.157	230	0.804	1403	0.147	1398	0.857	2805	0.142	2800	0.646	1978	0.128	1973	0.606

BEE

Model	Factors	Juveniles (1 - 20y)				Adults (20 - 60y)				Older Adults (60+ y)			
		β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p
4. BEE~Body Mass+Sex+Age	Intercept	2.965	0.158	18.785	0.000	3.649	0.104	34.943	0.000	5.905	0.379	15.571	0.000
	Body Mass	0.034	0.003	11.004	0.000	0.036	0.001	32.494	0.000	0.031	0.002	14.277	0.000
	Sex(M)	1.185	0.101	11.733	0.000	1.263	0.045	27.915	0.000	0.724	0.066	10.939	0.000
	Age	0.033	0.015	2.212	0.028	-0.008	0.002	-3.487	0.001	-0.041	0.004	-9.501	0.000
	model	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*
		345	0.848	341	0.581	1036	0.694	1032	0.682	621	0.761	617	0.520
		β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p
5. ln(BEE)~ln(FFM)+ln(FM)	Intercept	0.055	0.078	0.706	0.480	-0.954	0.059	-16.176	0.000	-0.923	0.099	-9.350	0.000
	ln FFM	0.535	0.028	19.103	0.000	0.707	0.016	45.353	0.000	0.656	0.027	24.640	0.000
	ln FM	-0.095	0.014	-6.784	0.000	0.019	0.006	3.408	0.001	0.028	0.015	1.819	0.069
	model	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*
		345	0.153	342	0.573	1036	0.103	1033	0.688	621	0.135	618	0.530
		β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p
6. ln(BEE)~ln(FFM)+ln(FM)+Sex+Ag	Intercept	-0.270	0.100	-2.704	0.007	-0.497	0.079	-6.281	0.000	-0.089	0.151	-0.587	0.557
	ln FFM	0.663	0.044	15.167	0.000	0.561	0.023	24.008	0.000	0.549	0.040	13.663	0.000
	ln FM	-0.054	0.014	-4.005	0.000	0.054	0.007	7.809	0.000	0.042	0.016	2.619	0.009
	Sex(M)	0.090	0.019	4.780	0.000	0.086	0.010	8.297	0.000	0.037	0.016	2.288	0.022
	Age	-0.018	0.003	-5.102	0.000	-0.001	0.000	-2.124	0.034	-0.006	0.001	-8.814	0.000
	model	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*
		345	0.137	340	0.658	1036	0.100	1031	0.708	621	0.128	616	0.582

AEE

Model	Factors	Juveniles (1 - 20y)				Adults (20 - 60y)				Older Adults (60+ y)			
		β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p
7. AEE~Body Mass+Sex+Age	Intercept	-0.481	0.237	-2.030	0.043	1.822	0.252	7.231	0.000	5.835	0.604	9.663	0.000
	Body Mass	0.032	0.005	6.774	0.000	0.023	0.003	8.870	0.000	0.014	0.003	4.111	0.000
	Sex(M)	0.999	0.152	6.581	0.000	1.308	0.109	11.983	0.000	0.661	0.105	6.264	0.000
	Age	0.113	0.022	5.133	0.000	-0.012	0.006	-2.216	0.027	-0.058	0.007	-8.354	0.000
	model	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*
		345	1.275	341	0.476	1036	1.675	1032	0.201	621	1.212	617	0.219
		β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p
8. ln(AEE)~ln(FFM)+ln(FM)	Intercept	-3.330	0.231	-14.447	0.000	-4.124	0.248	-16.627	0.000	-2.556	0.401	-6.381	0.000
	ln FFM	1.301	0.082	15.776	0.000	1.476	0.065	22.614	0.000	0.952	0.108	8.807	0.000
	ln FM	-0.099	0.041	-2.414	0.016	-0.142	0.023	-6.130	0.000	-0.042	0.062	-0.685	0.494
	model	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*
		338	0.445	335	0.550	1023	0.423	1020	0.333	612	0.546	609	0.116
		β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p
9. ln(AEE)~ln(FFM)+ln(FM)+Sex+Ag	Intercept	-3.437	0.332	-10.366	0.000	-5.194	0.342	-15.187	0.000	0.222	0.625	0.355	0.723
	ln FFM	1.349	0.145	9.295	0.000	1.816	0.100	18.079	0.000	0.674	0.165	4.088	0.000
	ln FM	-0.093	0.044	-2.097	0.037	-0.221	0.029	-7.598	0.000	-0.010	0.066	-0.151	0.880
	Sex(M)	0.006	0.062	0.090	0.928	-0.198	0.044	-4.480	0.000	0.079	0.067	1.181	0.238
	Age	-0.005	0.011	-0.474	0.636	0.002	0.001	1.162	0.246	-0.025	0.003	-7.852	0.000
	model	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*
		338	0.446	333	0.547	1023	0.420	1018	0.345	612	0.521	607	0.195

PAL

Model	Factors	Juveniles (1 - 20y)				Adults (20 - 60y)				Older Adults (60+ y)			
		β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p
10. PAL~Body Mass+Sex+Age	Intercept	1.290	0.048	26.913	0.000	1.668	0.041	40.739	0.000	2.209	0.144	15.348	0.000
	Body Mass	0.002	0.001	2.093	0.037	0.001	0.000	2.058	0.040	0.000	0.001	-0.239	0.811
	Sex(M)	0.050	0.031	1.641	0.102	0.094	0.018	5.312	0.000	0.058	0.025	2.298	0.022
	Age	0.022	0.004	4.933	0.000	-0.001	0.001	-1.260	0.208	-0.007	0.002	-4.142	0.000
	model	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*
		345	0.258	341	0.234	1036	0.272	1032	0.032	621	0.289	617	0.032
		β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p
11. PAL~ln(FFM)+ln(FM)	Intercept	0.420	0.129	3.252	0.001	0.174	0.148	1.178	0.239	1.215	0.212	5.736	0.000
	ln FFM	0.386	0.046	8.348	0.000	0.477	0.039	12.221	0.000	0.201	0.057	3.524	0.000
	ln FM	-0.019	0.023	-0.817	0.415	-0.098	0.014	-6.999	0.000	-0.085	0.033	-2.605	0.009
	model	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*
		345	0.253	342	0.263	1036	0.257	1033	0.137	621	0.291	618	0.021
		β	std.err.	t-value	p	β	std.err.	t-value	p	β	std.err.	t-value	p
12. PAL~ln(FFM)+ln(FM)+Sex+Age	Intercept	0.528	0.185	2.860	0.005	-0.744	0.200	-3.714	0.000	1.841	0.340	5.417	0.000
	ln FFM	0.338	0.081	4.179	0.000	0.777	0.059	13.140	0.000	0.164	0.090	1.814	0.070
	ln FM	-0.026	0.025	-1.034	0.302	-0.164	0.017	-9.442	0.000	-0.087	0.036	-2.405	0.016
	Sex(M)	-0.009	0.035	-0.250	0.803	-0.174	0.026	-6.645	0.000	0.000	0.037	0.007	0.995
	Age	0.006	0.006	0.873	0.384	0.000	0.001	0.497	0.619	-0.006	0.002	-3.818	0.000
	model	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*	*N*	*SEE*	*df*	*adjR2*
		345	0.253	340	0.261	1036	0.252	1031	0.171	621	0.288	616	0.040

Table S3. Adjusted TEE, Adjusted BEE, and Adjusted BEE_{TEE}. *Infant data from the literature, males and females pooled. N values for infant BEE (0 to 2 years) indicate number of entries and (number of individuals). See Methods.

Adjusted TEE - Female & Male Cohorts										Adjusted BEE and Adjusted BEE_{TEE}										
					Adjusted TEE								Adjusted BEE				Adjusted BEE_{TEE}			
Age	N		mean Age		F		M		N		mean Age		F		M		F		M	
Cohort	F	M	F	M	mean	sd	mean	sd	F	M	F	M	mean	sd	mean	sd	mean	sd	mean	sd
(0,0.5]	103	93	0.2	0.2	120.0	23.2	118.4	23.2	*22 (111)**		*0.2*		*100.47*	*33.89*			*86.03*	28.9		
(0.5,1]	18	23	0.7	0.7	139.8	17.0	145.5	25.7	*20 (88)**		*0.9*		*142.89*	*11.62*			*115.47*	9.2		
(1,2]	33	35	1.7	1.6	147.4	23.9	148.2	21.6	*18 (86)**		*1.6*		*142.02*	*13.52*			*111.94*	9.6		
(2,4]	54	48	3.8	3.8	147.0	13.4	150.3	19.6	3	1	3.8	4.0	150.2	6.0	###	NA	108.6	7.4	100.7	NA
(4,6]	99	121	5.3	5.3	142.5	14.0	148.2	18.5	9	5	5.7	5.4	156.4	26.3	###	30.9	110.1	19.9	108.1	19.9
(6,8]	42	42	7.0	7.2	139.2	16.7	143.2	13.6	18	12	7.2	7.4	136.9	25.8	###	21.8	94.6	17.7	94.6	15.1
(8,10]	79	75	9.1	9.1	132.8	19.2	140.2	18.7	22	16	9.2	9.5	130.0	23.4	###	21.8	87.2	15.2	88.8	14.2
(10,12]	68	34	11.1	11.0	122.0	23.4	133.4	16.3	5	5	11.1	11.1	128.3	19.9	###	21.2	82.6	12.3	81.8	15.0
(12,16]	229	128	14.4	14.5	113.1	22.9	118.9	21.4	18	16	14.4	13.9	103.1	18.6	###	23.3	64.9	12.2	82.4	15.7
(16,20]	209	103	18.3	18.4	107.1	14.4	113.3	17.1	155	148	18.5	18.9	97.5	12.9	###	7.5	60.2	8.1	62.9	5.3
(20,25]	252	123	23.2	23.5	100.6	15.5	106.7	21.9	135	116	23.4	23.8	98.3	10.5	99.6	8.1	60.6	7.1	57.0	5.2
(25,30]	280	182	27.8	28.0	100.5	15.3	102.0	21.2	115	104	27.9	27.9	100.8	11.5	###	13.4	62.5	7.8	59.6	8.3
(30,35]	235	146	33.0	32.8	100.0	11.9	100.7	16.5	96	94	33.2	33.1	98.7	9.7	###	10.4	60.9	6.3	59.7	7.0
(35,40]	231	165	38.0	38.0	100.0	11.9	102.3	16.3	112	110	38.1	38.2	99.7	10.2	###	11.7	61.4	6.9	59.1	7.2
(40,45]	301	165	42.8	42.9	101.3	12.6	100.8	13.2	100	96	42.9	42.6	99.8	10.4	###	9.1	61.6	6.9	59.7	6.1
(45,50]	171	144	47.4	47.8	102.0	12.4	100.5	14.3	42	41	47.3	48.1	99.0	14.7	###	14.6	61.4	9.6	62.7	8.9
(50,55]	105	93	52.8	52.6	100.5	11.4	100.8	13.2	33	33	53.1	53.4	96.1	9.1	###	9.2	59.8	5.5	60.3	5.9
(55,60]	111	76	58.2	57.8	102.2	11.7	102.9	20.0	23	23	58.1	57.5	100.3	9.5	###	7.1	62.5	6.1	57.9	4.5
(60,65]	252	90	63.2	63.2	98.8	12.4	99.8	15.3	23	21	62.4	63.1	99.5	12.8	99.2	8.5	62.6	8.3	58.3	5.2
(65,70]	387	90	68.0	68.0	97.6	10.9	94.4	11.1	40	40	68.0	68.7	91.0	8.6	95.2	7.6	56.9	5.9	56.4	4.8
(70,80]	681	232	75.1	75.4	93.9	12.1	90.6	14.6	188	173	75.2	75.4	86.8	9.9	86.4	12.9	55.2	6.6	51.5	8.0
(80,90]	149	66	83.6	84.2	87.6	12.2	82.8	13.0	47	38	84.1	84.0	86.5	16.0	78.6	10.8	55.3	10.8	47.6	6.8
(90,100]	22	8	94.4	94.0	73.2	12.4	76.0	9.6	14	5	94.9	94.0	91.2	19.1	94.8	14.6	57.1	12.9	57.3	8.6

Table S4. Segmented Regression Analyses

adjTEE	Segments				Break Points		
	beta	*SE*	*CI_lower*	*CI_upper*	*Estimate*	*CI_lower*	*CI_upper*
	84.70	7.15	70.69	98.71	0.69	0.61	0.76
	-2.77	0.07	-2.91	-2.63	20.46	19.77	21.15
	-0.02	0.02	-0.07	0.03	62.99	60.13	65.85
	-0.68	0.06	-0.79	-0.57			

adjBEE	Segments				Break Points		
	beta	*SE*	*CI_lower*	*CI_upper*	*Estimate*	*CI_lower*	*CI_upper*
	75.51	5.59	64.55	86.46	1.04	0.94	1.14
	-3.75	0.22	-4.17	-3.33	18.00	16.82	19.18
	0.02	0.05	-0.07	0.12	46.46	40.57	52.35
	-0.45	0.04	-0.53	-0.37			

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