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Fat-Free Mass and Total Daily Energy Expenditure Estimated using Doubly Labelled Water Predict Energy Intake in a Large Sample of Community-Dwelling Older Adults

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Abbreviations: DLW, doubly labelled water; EI, energy intake; FM, fat mass; FFM, fat-free mass; PA, physical activity; RMR, resting metabolic rate; TDEE, total daily energy expenditure.

ABSTRACT

BACKGROUND: Up to 30% of community-based older adults report reduced appetite and energy intake (EI), but previous research examining the underlying physiological mechanisms have focused on the mechanisms that suppress eating rather than the hunger drive and EI.

OBJECTIVE: To examine the associations between fat-free mass (FFM), physical activity (PA), total daily energy expenditure (TDEE) and self-reported EI in older adults.

METHODS: The present study was a secondary analysis of The Interactive Diet and Activity Tracking in AARP Study. Body composition (deuterium dilution), PA (accelerometry) and TDEE (doubly labelled water) were measured in 590 older adults (age = 63.1 ± 5.9 years; BMI = 28.1 ± 4.9 kg/m^2). Total daily EI was estimated from a single 24-hour dietary recall (EI_{single}; ± one month of PA and TDEE measurement) and the mean of up to six recalls over a 12-month period (EI_{mean}), with mis-reporters classified using the 95% confidence intervals between EI_{mean} and TDEE.

RESULTS: After controlling for age and sex, linear regression demonstrated that FFM and TDEE predicted EI when estimated from a single 24-hour dietary recall ($p < 0.05$), the mean of up to six dietary recalls ($p < 0.05$) and after the removal of those classified as under-reporters ($p < 0.001$). Age moderated the associations between FFM and EI_{single} ($p < 0.001$), FFM and EI_{mean} ($p < 0.001$), and TDEE with EI_{single} ($p = 0.016$), with associations becoming weaker across age quintiles.

CONCLUSIONS: These data suggest that total daily EI is proportional to FFM and TDEE, but not fat mass, in older adults. These associations may reflect an underling drive to eat that influences daily food intake. While the associations between FFM or TDEE and EI existed across all age quintiles, these associations weakened with increasing age.

Trial Registration: The Interactive Diet and Activity Tracking in AARP (IDATA) Study was registered at clinicaltrials.gov as: NCT03268577 (http://www.clinicaltrials.gov).

Key Words: Fat-free mass, total daily energy expenditure, appetite, energy intake, older adults.

INTRODUCTION

Up to 30% of community based older adults over the age of 65 years experience a loss of appetite, termed anorexia of aging, that increases their risk of malnutrition, sarcopenia, frailty, and mortality (1). Increased concentrations of anorectic hormones such as cholecystokinin, pancreatic peptide YY, leptin and insulin have been reported in studies comparing younger vs older adults (2), and when considered alongside reduced gastric motility and emptying (3), provide a mechanistic account for why older adults display earlier meal termination, reduced meal intake and greater post-prandial fullness (4). Importantly however, these appetitive signals act post-prandially to supress rather than to drive hunger and food intake. This distinction is necessary as older adults also demonstrate losses in the motivational drive to eat, as evidenced by reductions in perceived hunger. For example, a meta-analysis by Giezenaar et al. (4) reported that fasting hunger ratings were 25% lower in older vs. young adults. Attenuated fasting hunger cannot be explained by post-prandial satiety mechanisms, and a recent meta-analysis reported no differences between young and older adults in fasted or post-prandial concentrations of the orexigenic ‘hunger hormone’ ghrelin (total or acylated) (2). Consequently, while current scientific explanations provide a coherent account for the increased post-prandial satiety seen in older adults, there is a need to examine the specific physiological mechanisms that underlie sensations of hunger and the drive to eat in older adults.

Based on work conducted in young and middle-aged adults, we have proposed that the metabolic activity of fat-free mass (FFM) creates a long-term (tonic) drive to eat that ensures the energetic demands of key tissue-organs and metabolic processes are met (5-7). This model is based upon the existence of a fundamental relationship between energy expenditure and energy intake (EI), and shifts scientific attention from the mechanisms that supress hunger to those that drive hunger. Ourselves and others have reported positive associations between FFM, but not fat mass (FM), and subjective hunger, *ad libitum* meal intake and total daily EI (8-12). Findings have been confirmed in free-living studies in which participants were able to choose foods from their habitual diets (13, 14) and in a number of different populations (15-18). In considering the mechanism underlying these associations, it is relevant that FFM is the strongest determinant of resting metabolic rate (RMR), with RMR in turn, the strongest determinant of total daily energy expenditure (TDEE). Accordingly, it has been demonstrated the effect of FFM on EI is mediated statistically by RMR (19, 20) and TDEE (21), suggesting that energy expenditure *per se* may influence daily EI.

For a number of reasons, it is theoretically and clinically important to investigate whether these associations between FFM and EI exists in older adults. The loss of appetite with aging often exists in parallel with the development of sarcopenia and declines in RMR (22), and when coupled with age-related reductions in physical activity (PA), can lead to reductions in TDEE. Given the body of evidence described above, it can be hypothesised that a decline in FFM with aging could contribute to the reduced drive to eat and EI seen in this population. However, despite strong theoretical and logical appeal, there is little empirical evidence demonstrating that TDEE and its main determinants (e.g., FFM, RMR and PA energy expenditure) exert influence over food intake in older adults. An important first step is therefore to examine the relationships between FFM (and FM) and EI in a large sample of older adults in which measures of body composition and energy expenditure are available alongside measures of food intake. To this end, we analysed data from The Interactive Diet and Activity Tracking in AARP (IDATA) Study, a biomarker validation study of self-reported diet and PA measures in older adults (n = 1082; 50-74 years). The aim of our secondary analyses was to examine the associations between gold-standard measures of FFM (deuterium dilution), PA (tri-axial accelerometry), TDEE (doubly labelled water; DLW) and self-reported EI (with and without adjustment for under-reporting) in a sub-sample of data where relevant outcomes were available (n = 590).

METHODS

Participants and Study Design

The present paper was a secondary analysis of 590 participants from a total of 1082 participants enrolled in the IDATA Study (see **Table 1** for descriptive characteristics). The primary aim of the IDATA study was to evaluate how well internet-based, self-report instruments measure EI and PA levels and their relationship with disease, and it was registered at clinicaltrials.gov as: NCT03268577 (http://www.clinicaltrials.gov). In the present analyses, only participants with valid measures of body composition (deuterium dilution), PA (tri-axial accelerometry), TDEE (DLW) and EI (24-hour recall) were included. A participant flow diagram for the main IDATA study can be found in Supplementary Materials Figure 1, while a flow diagram detailing the inclusion/exclusion of participants used in the present analyses can be found in Supplementary Materials Figure 2. Participants were aged between 50-74 years, English speaking, not following a weight loss diet, had internet access, and were free from mobility limitations and major medical conditions (history of renal failure, congestive heart failure, or other conditions involving disturbances in fluid balance). Participants enrolled in the IDATA study were randomly assigned to 1 of 4 study groups to reduce seasonal variation in diet and PA and completed a 12-month assessment period (groups 1–4: n = 183, 192, 240, and 460, respectively). Data collection was identical for each group except that in Groups 1 and 3 TDEE and PA were measured during Month One while in Groups 2 and 4 these were measured in Month Six (see **Table 2**). Anthropometric measures were taken during clinical laboratory visits at Months One, Six and Twelve in all participants, while total daily EI was estimated bi-monthly using online 24-hour dietary recalls. All participants provided written consent and the study was approved by the National Cancer Institute Special Studies Institutional Review Board. Individuals who completed the study received $450. The present analyses were not part of the *a priori* outcomes of the IDATA study. Data were accessed through the Cancer Data Access System (https://cdas.cancer.gov/idata/) after project proposal approval by the National Cancer Institute (https://cdas.cancer.gov/approved-projects/1916/).

Table 1 here

Total Daily Energy Expenditure

Total daily energy expenditure was estimated over a 14-day period (month one for Groups 1 and 3, month six for Groups 2 and 4) using DLW as previously described (23). Following an overnight fast (>8hrs), participants provided a baseline urine sample and consumed orally a pre-prepared dose of $^2H_2{}^{18}O$ based on their body mass (2 g of 10 atom percent ^{18}O labelled water and 0.12 g of 99.9 atom percent deuterium labelled water per kg of estimated total body water). After consumption, participants provided an hourly urine sample for four hours. One hour after dosing, an 8-ounce (240 mL) can of meal-replacement beverage was provided. Participants could drink an additional 7 ounces (210 mL) of liquid over the next 4 h, with liquid intakes recorded. Two final urine samples were collected 14 days after the initial dosing day. Total daily energy expenditure was calculated using the equation of Racette et al. (24) and the modified Weir equation, assuming a respiratory quotient of 0.86 for all participants. Urine samples were analysed at the University of Wisconsin's Isotope Ratio Mass Spectrometry Core by using the isotope measurement method described in the OPEN study (23).

Table 2 here

Body Composition and Anthropometry

Total body water (kg) was determined by deuterium dilution with isotope dilution spaces (kg) calculated according to Coward and Cole (25). Total body water was calculated as the average of the deuterium dilution space divided by 1.041 and the oxygen dilution space divided by 1.007 to correct for in vivo isotope exchange (24). Fat-free mass was estimated as FFM (kg) = total body water/0.732, assuming a hydration factor of 0.732 and that total body fat is hydrophobic (26). Fat mass was estimated as body mass (kg) minus FFM (kg). Anthropometric measurements were taken at Months One, Six and Twelve, with body mass index calculated from height and weight (kg/m^2). For height and body mass measurements, the mean of two repeat readings at each clinical visit was used, with a third reading taken if significant differences between the first two readings existed.

Physical Activity

The measurement of PA, and its relationship to TDEE, have been described in detail elsewhere (27). Briefly, PA was measured using hip worn tri-axial accelerometers (ActiGraph GT3X) with participants asked to wear the device for seven consecutive days and only to remove it when showering, bathing, swimming and immediately prior to bed at night. Two 7-day PA collection periods were conducted in the IDATA study, but the present analysis only used the 7-day period corresponding to the month in which the DLW measurement was taken (Month One for Groups 1 and 3; Month Six for Groups 2 and 4). Mean activity counts per days (CPM/D) were calculated from the vector magnitude of the X, Y and Z axes using data averaged over 60 second epochs. A minimum of 10 hours of wear time was needed to constitute a valid measurement day (27), with the Choi algorithm (28) used to estimate non-wear time from vector magnitude data using the 'PhysicalActivity' package in Rstudio version 1.4.1717. A minimum of 4 valid days were required to be included in the present analysis, with participants having on average 6 valid days of accelerometer data and a mean wear time of 14.8 hrs per day.

Total Daily Energy Intake

Total daily EI was estimated in the IDATA study using six bi-monthly 24-hour dietary recalls during the 12-month study period (see Table 2). In the present analysis, total daily EI was estimated from a single dietary recall performed ± one month of PA and TDEE measurement (EI_{single}), and the mean of the six recalls (EI_{mean}) as the use multiple recalls has been shown to better reflect habitual food intake (29). For EI_{mean}, participants completed an average of 5.6 ± 0.8 dietary recalls. The ASA24, a web-based dietary assessment tool modelled on the USDA's Automated Multiple-PASS Method for 24-hour dietary recalls (30), was used to estimate EI. Participants were asked via e-mail to complete six ASA24s, each unannounced and on a randomly assigned day, approximately every other month. If a participant did not complete the requested ASA24 within 24 hours of e-mail notification, a reminder e-mail was sent on a new randomly selected day. Participants were provided 3 attempts to complete each of the required 6 dietary recalls. Nutrient and food group intakes in the ASA24 were estimated by using the USDA's Food and Nutrient Database for Dietary Studies, version 4.1; MyPyramid Equivalents Database, version 2.0; and the NHANES Dietary Supplement Database 2007–2008. The IDATA study also included 4-day food records and a food frequency questionnaire, but these were not closely aligned with PA or TDEE measurement and the ASA24 has previously been shown to provide the best estimate of total daily EI relative to TDEE in these data (31).

Mis-Reporting of Total Daily Energy Intake

Dietary mis-reporting was examined using the 95% confidence intervals between EI_{mean} and DLW-derived TDEE based on the methods proposed by Black et al. (32):

- $95\%\ CL = 2 \times sqrt[(CV_{wEI}{}^2/d) + CV_{wEE}{}^2 - 2r \cdot (CV_{wEI}/d) \cdot CV_{wEE}]$

Where d is the number of days of diet assessment, r is the Pearson's correlation coefficient between DLW-derived TDEE and EI_{mean}, the mean coefficient of EI variation (CV_{wEI}) was assumed to be 23% and the coefficient of variation for DLW energy expenditure (CV_{wEE}) was assumed to be 8.2% based on the values proposed by Black et al. (32). Acceptable reporters were defined as having an EI:TDEE ratio between 0.77-1.23, under-reporters as having a ratio EI:TDEE <0.77, and over-reporters as an EI:TDEE ratio >1.23.

Statistical Analysis

Statistical analyses were performed using Rstudio version 1.4.1717 and data are reported as mean ± SD. Independent two sample Welch's t-tests were used to examine for differences between males and female. Paired t-tests were used to examine for differences between EI_{single} and EI_{mean} and between EI and TDEE. Bland and Altman plots were also used to compare the difference between EI_{single} or EI_{mean} and TDEE using the 'blandr' package in Rstudio. Pearson's correlations were used to examine the associations between body composition, PA and TDEE with EI_{single} or EI_{mean}. As age-related changes in FFM, PA and TDEE may accelerate during later life (33, 34), moderation analyses using PROCESS for SPSS (version 3.2) (35) was used to examine whether age moderated the associations between FFM or TDEE and EI, with Pearson's correlations repeated in each separate age quintile (see Supplementary Materials Table 1 for descriptive characteristics by age quintiles). Linear regression was used to examine for predictors of EI based on our previous findings in young and middle aged adults (5-7). In Models 1-3 EI_{single} was used as the dependent variable, with FM and FFM entered as independent variables in Model 1, FM, FFM and PA in Model 2, and FM, FFM, PA and TDEE in Model 3. The same models were repeated using EI_{mean} as the dependent variable (models 4-6), and following removal of participants classified as under-reporters (models 7-9). Given their known effects on FFM, TDEE and EI, sex and age were included in all regression models. As body weight was measured on three occasions during the study (months 1, 6 and 12; mean change = -0.22 ± 3.59 kg), weight change was also initially added as a predictor of EI. However, weight change did not predict EI or influence the associations between the remaining predictors, and therefore was not included. Visual inspection of model residual Q-Q plots confirmed no serious violations of normality, while linearity was confirmed via visual inspection of residual plots and homoscedasticity via Scale-Location plot inspection. Multicollinearity was assessed using the variance inflation factor (VIF), which indicated that there was no instability in any of the models with VIF scores <6.43 for all predictors included (36). Examination of Cook's Distance indicated the presence of 4 influential outliers in 1 or more of regression models 1-6 (Cook's Distance > 0.5 and a standardised residual >4.0). Therefore, these individuals were removed and regression analyses conducted in 586 individuals in these models. Their removal did not alter interpretation of model estimates or outcomes, but did result in a small increase in explained variance (increase in adj R^2 between 0.6 to 1.5%). To account for differences in FM and FFM due to height, regression analyses were also repeated using the FM (FM/height^2) and FFM (FFM/height^2) indexes, but main outcomes again did not differ (see Supplementary Materials Table 2).

RESULTS

Participant descriptive characteristics can be found in Table 2. As would be expected, FFM was higher in males than females ($t_{(529.5)} = 28.2$, $p < 0.001$), but FM did not differ by sex ($t_{(588)} = 1.8$, $p = 0.064$). Males were less active than female ($t_{(586.3)} = 3.1$, $p = 0.002$), but TDEE was higher in males ($t_{(550.1)} = 17.5$, $p < 0.001$). Total daily EI did not differ when estimated from a single 24-hour dietary recall (EI_{single}) or based on the mean of six recalls (EI_{mean}; 9.3 ± 587 kcal/day; $t_{(589)} = 0.4$, $p = 0.699$). Both EI_{single} ($t_{(578.9)} = 6.4$, $p <$

0.001) and EI_{mean} ($t_{(568.5)} = 10.2$, $p < 0.001$) were higher in males than females. When EI was compared to TDEE, EI_{single} was -321 ± 841 kcal/day ($t_{(589)} = 9.3$, $p < 0.001$) lower than TDEE, while EI_{mean} was -312 ± 622 kcal/day lower ($t_{(589)} = 12.2$, $p < 0.001$). Limits of agreement between EI and TDEE were smaller with EI_{mean} (**Figure 1**), with the lower and upper limits of agreement for EI_{single} -1327 (95% CI = -1443 to -1211) and 1971 kcal/day (95% CI = 1854 to 2087), respectively, as compared to -907 (95% CI = -821 to -993) and 1532 (95% CI = 1446 to 1618), respectively.

Figure 1 here

Associations between Body Composition, Physical Activity and Total Daily Energy Expenditure

EI_{single} and EI_{mean} were positively associated with FFM ($r = 0.29$, $p < 0.001$; $r = 0.45$, $p <0.001$, respectively;) and TDEE ($r = 0.31$, $p < 0.001$; $r = 0.42$, $p <0.001$, respectively), but not FM ($r = -0.01$, $p = 0.814$; $r = -0.05$, $p = 0.427$, respectively) or PA ($r = 0.07$, $p = 0.075$; $r = 0.03$, $p = 0.470$, respectively; see **Figure 2**). To test whether the strength of these associations varied with age, moderation analysis was conducted. An interaction was found in which age ($\beta = -0.001$, $p = 0.002$; $\beta = 0.001$, $p = 0.045$, respectively) moderated the association between FFM and EI_{single} ($F_{(3, 586)} = 21.57$, $R^2 = 0.10$, $p < 0.001$) or EI_{mean} ($F_{(3, 586)} = 50.69$, $R^2 = 0.21$, $p < 0.001$), with the strength of associations between FFM and EI_{single} becoming weaker across age quintile 1 ($r = 0.45$; $p < 0.001$), quintile 2 ($r = 0.33$; $p < 0.001$), quintile 3 ($r = 0.23$; $p = 0.013$), quintile 4 ($r = 0.22$; $p = 0.018$) and quintile 5 ($r = 0.21$; $p = 0.022$). Similarly, the association between FFM and EI_{mean} was also weaker across age quintile 1 ($r = 0.56$; $p < 0.001$), quintile 2 ($r = 0.44$; $p < 0.001$), quintile 3 ($r = 0.42$; $p < 0.001$), quintile 4 ($r = 0.40$; $p < 0.001$) and quintile 5 ($r = 0.38$; $p < 0.001$). An interaction was also found in which age ($\beta = -0.009$, $p = 0.016$) moderated the association between TDEE and EI_{single} ($F_{(3, 586)} = 23.96$, $R^2 = 0.11$, $p < 0.001$), with the strength of association with EI_{single} again weakening across age quintile 1 ($r = 0.42$; $p < 0.001$), quintile 2 ($r = 0.35$; $p < 0.001$), quintile 3 ($r = 0.25$; $p = 0.007$), quintile 4 ($r = 0.28$; $p = 0.002$) and quintile 5 ($r = 0.23$; $p = 0.012$). Age did not moderate ($\beta = -0.005$, $p = 0.146$) the association between TDEE and EI_{mean} ($F_{(3, 586)} = 44.74$, $R^2 = 0.19$, $p < 0.001$), although the associations between TDEE and EI_{mean} did became weaker across age quintile 1 ($r = 0.52$; $p < 0.001$), quintile 2 ($r =$

0.41; $p < 0.001$), quintile 3 ($r = 0.42$; $p < 0.001$), quintile 4 ($r = 0.37$; $p < 0.001$) and quintile 5 ($r = 0.38$; $p < 0.001$).

Figure 2 here

Body Composition, Physical Activity and Total Daily Energy Expenditure as Predictors of Total Daily Energy Intake

To examine the relationships between body composition, PA, TDEE and EI_{single}, three linear regression models were examined (**Table 3**). In Model 1 ($F_{(4, 581)} = 16.15$, $p < 0.001$; adj $R^2 = 0.093$), FFM ($\beta = 0.30$; $p < 0.001$) and FM ($\beta = -0.10$; $p = 0.044$) predicted $EI_{single,}$ but age and sex were not predictors. The addition of PA in Model 2 explained a further 0.8% of variance ($F_{(5, 580)} = 14.14$, $p < 0.001$; adj $R^2 = 0.101$), with FFM ($\beta = 0.33$; $p < 0.001$) and PA ($\beta = 0.10$; $p = 0.018$), but not FM, independently predicting EI_{single}. When TDEE was added (Model 3; $F_{(6, 579)} = 12.74$, $p < 0.001$; adj $R^2 = 0.105$), FFM ($\beta = 0.19$; $p = 0.049$) and TDEE ($\beta = 0.15$; $p = 0.022$) predicted EI_{single}. When these models were repeated using EI_{mean} as the dependent variable (Models 4-6), FFM ($\beta = 0.46$; $p < 0.001$) and FM ($\beta = -0.10$; $p = 0.026$) were again found to predict EI_{mean}, but not age and sex (Model 4; $F_{(4, 581)} = 43.88$, $p < 0.001$; adj $R^2 = 0.227$). Similarly, when PA was added, FFM ($\beta = 0.48$; $p < 0.001$) and PA ($\beta = 0.09$; $p = 0.033$) predicted EI_{mean} (Model 5; $F_{(4, 580)} = 36.23$, $p < 0.001$; adj $R^2 = 0.231$), but with the addition of TDEE (Model 6; $F_{(6, 579)} = 30.99$, $p < 0.001$; adj $R^2 = 0.235$), only FFM ($\beta = 0.37$; $p < 0.001$) and TDEE ($\beta = 0.12$; $p = 0.049$) predicted EI_{mean}.

Table 3 here

Mis-Reporting of Total Daily Energy Intake

Based on the 95% confidence limits of agreement between EI_{mean} and TDEE, 205 individuals were classified as under-reporters. Removal of under-reporters did not alter the associations between body composition, PA, TDEE and EI_{mean} (Table 3; Models 7-9), with FFM ($\beta = 0.39$; $p < 0.001$) and TDEE ($\beta = -0.18$; p <

0.001) remaining independent predictors of EI_{mean} when included alongside age, sex, FM and PA ($F_{(6, 378)}$ = 58.49, p < 0.001; adj R^2 = 0.473; Model 9).

DISCUSSION

This study examined the associations between body composition, PA, TDEE and EI in a large sample of older adults to provide insight into the factors that drive rather than supress food intake in this population. Consistent with our work in younger adults (5-7), FFM and TDEE, but not FM, were positively associated with self-reported EI. These associations between FFM and TDEE with EI remained consistent across models based on EI estimates from a single 24-hour dietary recall (Model 3), the mean of up to six dietary recalls (Model 6), and after the removal of those classified as under-reporters (Model 9). While FFM and TDEE were associated with EI across all age quintiles, the strength of these associations was moderated by age and decreased in strength across age quintiles. Our findings provide evidence that FFM and TDEE are associated with EI in older adults, and suggest that daily EI is proportional to the amount of FFM and TDEE, but not FM, in older adults.

Fat-Free Mass and Total Daily Energy Expenditure as Predictors of Energy Intake

In line with previous work in young and middle-aged adults (8-12), we demonstrate here that FFM and TDEE, but not FM, were positively associated with EI in this sample of older adults, suggesting that the amount of FFM and TDEE is proportional to daily EI in older adults. We have previously proposed that such findings reflect an underlying long-term or tonic drive to eat that ensures the energetic demands of key tissue-organs (e.g., FFM) and metabolic processes (e.g., RMR) are met through daily food intake (5-7). As an important determinant of RMR and TDEE, this positions FFM as a key feature of homeostatic appetite control that operates alongside adipose and gastro-intestinal satiety signals in the overall expression of appetite and food intake. It has been suggested that the lower levels of hunger and EI seen in older adults may reflect age-related changes in energy requirements subsequent to reductions in FFM, RMR and PA energy expenditure (37). While this implies some form of 'coupling' between the demand for energy arising from the biological processes and behavioural activities of daily living and EI, there is currently little empirical evidence that TDEE or its main determinants influence appetite or food intake in older adults. Indeed, we are aware of one study in which direct associations between FFM and appetite and EI have been demonstrated in older adults, with Johnson et al. (38) reporting that the change in FFM (+1.2 kg) following 12 weeks of resistance exercise and protein supplementation was associated with the change in EI (+119 kcal) during an *ad libitum* test meal (r = 0.53). Limited cross-sectional evidence also exists linking impaired appetite in older adults to reduced lean tissue mass and/or sarcopenia (39-42), but such studies are typically reliant on questionnaires (often with dichotomous yes/no questions) designed to quantify malnutrition (e.g., SNAQ, MUST, MNA-SF) rather than objective measures of appetite or food intake. However, as age-related appetite impairment reflects multi-factorial biological, psycho-social, environmental factors, and disease states and associated treatment (1), longitudinal studies that track changes in body composition and energy expenditure alongside appetite and EI are needed to establish a causal role for FFM and TDEE in the control of appetite of older adults and its dysregulation with aging.

In the present study PA was also found to predict EI, but its effect was modest and only explained 1-4% of the variance in EI when included alongside age, sex, FM and FFM. Further, when TDEE was added to these regression models, TDEE typically displaced PA as a predictor of EI. These findings, which are in agreement with our previous work in which activity energy expenditure predicted daily EI in free-living adults (accounting for 3% of the variance in total daily EI) (14), suggest that the energetic cost of PA may also influence EI via its contribution to TDEE, albeit more modestly than FFM or RMR. This modest contribution is perhaps not surprising given the smaller and more variable contribution of PA energy expenditure to TDEE as compared to FFM or RMR (43). In a recent publication using the present IDATA dataset examining Pontzer's hypothesis of constrained TDEE (44), a positive linear relationship was found between PA and TDEE across the entire cohort (27). It has previously been suggested that increasing PA would be a viable means of increasing appetite and EI in older adults, but the effect of exercise and/or PA on the mechanisms that control appetite in older adults is unclear (45).

Differences in the Strength of the Associations with Increasing Age

The associations between FFM and TDEE with EI were found to exist across all age quintiles, but the strength of these associations was moderated by age and decreased between the youngest and oldest age quintiles (~55 vs 71 years). These data suggest that while daily EI is proportional to TDEE and its main determinants in older adults, the influence of FFM and TDEE on daily food intake may weaken with increasing age. In keeping with these findings, age-related changes in FFM, RMR and TDEE are non-linear and may accelerate during later life (33, 34), and these physiological and functional changes are exacerbated by energy-protein malnutrition. When considered alongside our previous studies (5-7), the present findings raise the question of whether a bi-directional relationship exists between FFM loss and appetite impairment in older adults, with FFM loss potentially weakening the homeostatic drive to eat and further exaggerating FFM loss due to under-nutrition. Again however, causation cannot be inferred from the present data. It should also be noted that while the associations between FFM or TDEE weakened across age quintiles, no differences in EI existed between quintiles (either in the whole dataset or after removal of under-reporters). This lack of difference in EI might be because the proportion of males, who on average have higher EIs, increased in the older age quintiles (34% in the youngest quintile vs 62% in the oldest). Participants in the IDATA study were also free from major disease and comparatively active (PAL = 1.66 x RMR in males and 1.69 x RMR in females). Therefore, the clinical importance of any weakening in the associations between FFM or TDEE and EI remains to be determined. In the present data FM was not a predictor of EI when included alongside FFM, PA and TDEE, which is consistent with previous studies that report positive association between FFM and EI but a weak negative or no associations between FM and EI (9, 11, 13, 14). It has been suggested that adipose tissue accumulation may disrupt the coupling between FFM and EI, with associations between FFM and EI weaker in those living with obesity than lean individuals (12, 18, 21, 46). While age moderated the associations between FFM or TDEE and EI in the present study, FM was not a moderator of these associations (data not reported). This may be because participants in the current study were non-obese and that FM did not differ between age quintiles.

Under-Reporting of Total Daily Energy Intake

As multiple 24-hour dietary recalls provide a better approximation of habitual EI than single recalls (29), we estimated EI from a single recall closely aligned to the measures of PA and TDEE, and the mean of up to six recalls over the 12-month study period. Total daily EI did not differ between these two estimates, but the between-subject variation in EI was lower when using multiple recalls (e.g., smaller SD and limits of agreement). This may account for why the explained variance in EI was modest when EI was estimated from a single 24-hour dietary recall (adj R^2 = 11%; Model 3), but increased when EI was estimated using the mean of six dietary recalls (adj R^2 = 24%; Model 6). This magnitude of explained variance is consistent with previous studies using self-reported EI to examine the associations between FFM and EI (47). When those classified as under-reporters were removed, the amount of explained variance further increased (adj R^2 = 47%; Model 9) and was consistent with that reported in studies examining these associations using laboratory-based measures of EI (19). It should be noted though that the classification of individuals as under-reporters was in part based on the strength of association between TDEE and EI (alongside the coefficient of variation for EI and TDEE). This classification approach therefore likely resulted in a stronger association between EI and TDEE in the remaining sample, contributing to the increase in explained variance in models 7-9 alongside the removal of implausible EIs. It has been suggested that excluding participants based on statistical cut-offs of mis-reporting may introduce selection biases that alter the nature of the underlying associations examined (47). In the present data FFM and TDEE predicted EI across models based on both single or multiple 24-hour dietary recalls and with or without removal of under-reporters. This consistency across models suggests the nature of the associations between FFM and TDEE with EI were robust, but findings need to be replicated using objective laboratory measure of EI.

Strengths and Limitations

This study used a large sample of older adults to examine the associations between body composition, PA and TDEE with EI using gold standard measures of FFM, PA and TDEE. Findings that FFM and TDEE were predictors of EI in these data are consistent with previous findings and provide further evidence that the relationship between FFM and EI exists across the entire age spectrum from birth (16), through childhood and adolescence (15) and into adulthood (8-12). It has been previously reported that FFM is associated with subjective ratings of hunger and fullness (10, 11), but measures of appetite were not available in the current dataset. Instead, findings are based on self-reported EI, and as would be expected, our analysis indicated that under-reporting of EI was present. Importantly however, FFM and TDEE consistently predicted EI across models with and without removal of under-reporters, and such findings are consistent with studies using laboratory measured EI (8-12). While intake-balance methods can used to calculate objective estimates of EI, this approach was not appropriate here as the input variables needed to calculate EI (e.g., TDEE and changes in FFM/FM or body weight) were the same as those used as predictors of EI in the current analyses. The testing schedule employed in the IDATA study meant that the time-period in which the measures were taken did not always coincide (see Table 2). In the present analyses we selected measures that most closely aligned with one another, with PA, body composition and TDEE measured in the same month while EI_{single} was assessed ± one month of these measures. It also is important to note that these analyses were cross-sectional with body composition and TDEE measured on a single occasion. Therefore, these data cannot provide insight into the temporal patterns or causal relationships between age-related losses in FFM or TDEE and appetite and EI. The sample used in the present analysis also had a greater proportion of males than females (n = 301 vs. 289, respectively), and this was further exacerbated with the removal of under-reporters (n = 221 vs 164, respectively). While the original IDATA was balanced in terms of sex, a greater number of females were removed in the present analysis due to missing or incomplete PA and EI data (see Supplementary Figure 2).

Conclusions

Our findings provide evidence that FFM and TDEE are associated with EI in older adults, and consistent with previous findings in young adults, suggest that total daily EI is proportional to the amount of FFM and TDEE (but not FM) in older adults. These associations between FFM and TDEE with EI may reflect an underlying drive to eat that influences daily food intake in older adults. While the associations between FFM or TDEE and EI were found to exist across all age quintiles, these associations weakened with increasing age and future research should examine the potential for a bi-directional relationship between FFM loss and appetite impairment with aging. When considered alongside existing understanding of age-related changes in post-prandial satiety signalling and gastric motility/emptying, such data would provide a stronger account of the physiological mechanisms that underlie the drive and inhibition of appetite in older adults and its dysregulation with aging.

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MH analysed the data, wrote the initial manuscript, and had primary responsibility for final content. NC, RJS, GF and JEB contributed to the interpretation of data and edited the manuscript. All authors read and approved the final manuscript.

Data described in the manuscript are publicly and freely available upon request via the National Cancer Institute Access System (https://cdas.cancer.gov/idata/).

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FIGURE LABELS

Figure 1: Bland and Altman plot illustrating the difference between total daily energy intake estimated from a single 24-hour recall (Panel A) or the mean of six 24-hour recalls (Panel B) and total daily energy expenditure (doubly labelled water) against the mean of the two measures (n = 590).

TDEE, total daily energy expenditure; EI_{single}, total daily energy intake estimated from a single dietary 24-hour recall; EI_{mean}, total daily energy intake estimated from the mean of up to six 24-hour dietary recalls. The dashed black horizontal line represents the mean bias between the two methods, and the two solid grey horizontal lines represent the lower and upper 95% limits of agreement. For Panel A, the mean bias was -321 kcal/day, with the lower and upper limits of agreement -1327 and 1971 kcal/day, respectively. For Panel B, the mean bias was -312 kcal/day, with the lower and upper limits of agreement -907 and 1532 kcal/day, respectively.

Figure 2: Associations between total daily energy intake estimated from the mean of up to six 24-hour dietary recalls and fat mass (Panel A), fat-free mass (Panel B), physical activity (Panel C) and total daily energy expenditure (Panel D) (n = 590).

Note, total daily energy intake estimated from the mean of up to six 24-hour dietary recalls. Linear regression line with 95% confidence intervals (shaded bands) added to illustrate the association between variables.

Table 1: Participant characteristics (mean ± SD) for the whole sample and after removal of those classified as under-reporters based on the 95% confidence intervals between EI_{mean} and total daily energy expenditure.

	Whole sample	**Males**	**Females**	**After Removal of under-reporters**	**Males**	**Females**
N =	590	301	289	385	221	164
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age (yrs)	63.1 ± 5.9	64.2 ± 5.6	61.9 ± 5.9	63.6 ± 6.0	64.5 ± 5.73	62.6 ± 6.1
Height (m)	1.70 ± 0.9	1.76 ± 0.07	1.63 ± 0.06	1.70 ± 0.8	1.76 ± 0.07	1.63 ± 0.07
Body mass (kg)	81.6 ± 17.2	89.0 ± 16.3	73.9 ± 14.7	80.0 ± 16.3	87.2 ± 14.7	72.3 ± 14.4
BMI (kg/m^2)	28.1 ± 4.9	28.5 ± 4.6	27.6 ± 5.1	27.76 ± 4.6	28.1 ± 4.2	27.1 ± 5.0
Physical Activity (CPM/D)	683 ± 248	653 ± 258	715 ± 234	674 ± 245	638 ± 258	712 ± 226
Fat mass (kg)	30.6 ± 10.5	29.9 ± 10.7	31.5 ± 12.0	29.7 ± 9.6	29.0 ± 9.2	30.5 ± 10.1
Fat-free mass (kg)	51.0 ± 11.1	59.2 ± 8.5	42.4 ± 9.7	50.3 ± 10.5	58.2 ± 7.4	41.9 ± 5.47
TDEE (kcal/day)	2476 ± 520	2773 ± 481	2167 ± 353	2386 ± 467	2665 ± 399	2088 ± 330
EI_{single} (kcal/day)	2154 ± 841	2364 ± 878	1936 ± 743	2366 ± 835	2559 ± 860	2160 ± 756
EI_{mean} (kcal/day)	2164 ± 627	2401 ± 639	1916 ± 508	2406 ± 578	2641 ± 591	2156 ± 443

N; number of participants, BMI; body mass index, TDEE; total daily energy expenditure, CPM/D; counts per minute per day, EI_{single}; total daily energy intake estimated from a single 24-hour dietary recall, EI_{mean}, total daily energy intake estimated from the mean of up to six 24-hour dietary recalls.

Table 2: Timing of measurements in Groups 1 to 4 during the 12-month data collection period of the IDATA study.

	Month 1	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**
Groups One & Three												
TDEE (DLW)	■											
Physical Activity	■											
Energy Intake		■		■		■		■		■		■
Anthropometry	■					■						■
Groups Two & Four												
TDEE (DLW)						■						
Physical Activity						■						
Energy Intake	■		■		■			■		■		■
Anthropometry	■					■						■

DLW; doubly labelled water, TDEE; total daily energy expenditure. Groups 1–4: *n* = 183, 192, 240, and 460, respectively. Of note, EI_{single} was calculated from the 24-hour dietary recall performed in Month 1 for Groups One and Three, and Month 5 for Groups Two and Four.

Table 3: Regression coefficients showing the effects of age, sex, body composition, physical activity and total daily energy expenditure on self-reported total daily energy intake when estimated from a single 24-hour recall (Models 1-3), the mean of up to six 24-hour recalls (Models 4-6), and after removal of individuals classified as under-reporters (Models 7-9).

WHOLE SAMPLE												
EI_{single} (n = 586)	**Model 1 Adj R^2 = 0.09**				**Model 2 Adj R^2 = 0.10**				**Model 3 Adj R^2 = 0.11**			
	Estimate	**SE**	***β***	**P value**	**Estimate**	**SE**	***β***	**P value**	**Estimate**	**SE**	***β***	**P value**
Predictor												
Intercept	1132.1	448.1	-	0.018	661.4	488.6	-	0.176	627.8	487.1	-	0.197
Age (yrs)	0.67	5.7	-0.005	0.906	3.1	5.7	0.02	0.588	3.3	5.7	0.02	0.554
Sex	38.8	119.8	0.02	0.745	32.3	119.3	0.02	0.787	49.4	119.1	0.03	0.679
FM (kg)	**-7.3**	**3.6**	**-0.10**	**0.044**	-6.1	3.6	-0.08	0.098	-5.6	3.6	-0.07	0.121
FFM (kg)	**22.5**	**5.52**	**0.30**	**<0.001**	**24.3**	**5.7**	**0.33**	**<0.001**	**14.2**	**7.2**	**0.19**	**0.049**
PA (CPM/D)					**0.32**	**0.1**	**0.10**	**0.018**	0.2	0.1	0.06	0.164
TDEE (kcal/day)									**0.2**	**0.1**	**0.15**	**0.022**
EI_{mean} (n = 586)	**Model 4 Adj R^2 = 0.23**				**Model 5 Adj R^2 = 0.23**				**Model 6 Adj R^2 = 0.24**			
	Estimate	**SE**	***β***	**P value**	**Estimate**	**SE**	***β***	**P value**	**Estimate**	**SE**	***β***	**P value**
Predictor												
Intercept	1060.5	305.9	-	<0.001	770.3	333.8	-	0.022	750.4	333.2	-	0.025
Age (yrs)	-1.1	3.9	-0.01	0.786	0.5	3.9	0.004	0.908	0.6	3.9	0.00	0.875
Sex	50.6	81.8	0.04	0.536	46.6	81.5	0.04	0.568	56.7	81.5	0.05	0.487
FM (kg)	**-5.5**	**2.5**	**-0.10**	**0.026**	-4.8	2.5	-0.08	0.056	-4.5	2.5	-0.08	0.069
FFM (kg)	**25.6**	**3.9**	**0.46**	**<0.001**	**26.4**	**3.9**	**0.48**	**<0.001**	**20.4**	**4.9**	**0.37**	**<0.001**
PA (CPM/D)					**0.28**	**0.2**	**0.09**	**0.033**	0.1	0.1	0.05	0.198
TDEE (kcal/day)									**0.1**	**0.1**	**0.12**	**0.049**
REMOVAL OF UNDER-REPORTERS												
EI_{mean} (n = 385)	**Model 7 Adj R^2 = 0.37**				**Model 8 Adj R^2 = 0.39**				**Model 9 Adj R^2 = 0.47**			
	Estimate	**SE**	***β***	**P value**	**Estimate**	**SE**	***β***	**P value**	**Estimate**	**SE**	***β***	**P value**
Predictor												

Intercept	869.4	338.7		0.010	269.8	360.5		0.455	141.9	336.7		0.674
Age (yrs)	-5.0	4.1	-0.05	0.229	-2.0	4.1	-0.02	0.623	-1.8	3.8	-0.01	0.645
Sex	**-221.3**	**94.1**	**-0.20**	**0.019**	**-200.9**	**92.2**	**-0.17**	**0.029**	**-212.1**	**86.0**	**-0.18**	**0.015**
FM (kg)	**-6.8**	**3.1**	**-0.11**	**0.029**	-3.9	3.1	-0.07	0.202	-4.4	2.9	-0.07	0.131
FFM (kg)	**43.2**	**4.7**	**0.78**	**<0.001**	**43.8**	**4.6**	**0.79**	**<0.001**	**21.4**	**5.2**	**0.39**	**<0.001**
PA (CPM/D)					**0.4**	**0.1**	**0.18**	**<0.001**	0.1	0.1	0.05	0.240
TDEE (kcal/day)									**0.6**	**0.1**	**0.49**	**<0.001**

FM; fat mass, FFM; fat-free mass, PA; physical activity, TDEE; total daily energy expenditure, CPM/D; counts per minute per day, EI_{single}; total daily energy intake estimated from a single 24-hour dietary recall, EI_{mean}, total daily energy intake estimated from the mean of up to six 24-hour dietary recalls. Linear regression used to examine the effects of age, sex, body composition, physical activity and total daily energy expenditure on daily energy intake. In Models 1-3 EI_{single} used as the dependent variable, with FM and FFM entered as independent variables in Model 1, FM, FFM and PA in Model 2, and FM, FFM, PA and TDEE in Model 3. The same models were repeated using EI_{mean} as the dependent variable (models 4-6), and following removal of under-reporters (models 7-9). Given their known effects on FFM, TDEE and EI, sex and age were included in all regression models.