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**Article:**

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<https://doi.org/10.1093/jn/nxab434>

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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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### **Sources of Support for the Work:**

None.

### **Conflict of Interest and Funding Disclosure:**

Mark Hopkins- no conflicts of interest.

Nuno Casanova- no conflicts of interest.

Graham Finlayson- no conflicts of interest.

R James Stubbs- no conflicts of interest.

John E Blundell- no conflicts of interest.

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**Word Count:** 4932

**Number of Figures:** 2

**Number of Tables:** 3

**Supplementary Material:** 4

**Running Heading:** The drive to eat in older adults

**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.

1 **ABSTRACT**

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

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

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

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

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

22

23 **Trial Registration:** The Interactive Diet and Activity Tracking in AARP (IDATA) Study was registered  
24 at clinicaltrials.gov as: [NCT03268577](https://www.clinicaltrials.gov/ct2/show/study/NCT03268577) (<http://www.clinicaltrials.gov>).

25

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

## 27 INTRODUCTION

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

43

44 Based on work conducted in young and middle-aged adults, we have proposed that the metabolic activity  
45 of fat-free mass (FFM) creates a long-term (tonic) drive to eat that ensures the energetic demands of key  
46 tissue-organs and metabolic processes are met (5-7). This model is based upon the existence of a  
47 fundamental relationship between energy expenditure and energy intake (EI), and shifts scientific attention  
48 from the mechanisms that suppress hunger to those that drive hunger. Ourselves and others have reported  
49 positive associations between FFM, but not fat mass (FM), and subjective hunger, *ad libitum* meal intake  
50 and total daily EI (8-12). Findings have been confirmed in free-living studies in which participants were  
51 able to choose foods from their habitual diets (13, 14) and in a number of different populations (15-18). In

52 considering the mechanism underlying these associations, it is relevant that FFM is the strongest  
53 determinant of resting metabolic rate (RMR), with RMR in turn, the strongest determinant of total daily  
54 energy expenditure (TDEE). Accordingly, it has been demonstrated the effect of FFM on EI is mediated  
55 statistically by RMR (19, 20) and TDEE (21), suggesting that energy expenditure *per se* may influence  
56 daily EI.

57  
58 For a number of reasons, it is theoretically and clinically important to investigate whether these associations  
59 between FFM and EI exists in older adults. The loss of appetite with aging often exists in parallel with the  
60 development of sarcopenia and declines in RMR (22), and when coupled with age-related reductions in  
61 physical activity (PA), can lead to reductions in TDEE. Given the body of evidence described above, it can  
62 be hypothesised that a decline in FFM with aging could contribute to the reduced drive to eat and EI seen  
63 in this population. However, despite strong theoretical and logical appeal, there is little empirical evidence  
64 demonstrating that TDEE and its main determinants (e.g., FFM, RMR and PA energy expenditure) exert  
65 influence over food intake in older adults. An important first step is therefore to examine the relationships  
66 between FFM (and FM) and EI in a large sample of older adults in which measures of body composition  
67 and energy expenditure are available alongside measures of food intake. To this end, we analysed data from  
68 The Interactive Diet and Activity Tracking in AARP (IDATA) Study, a biomarker validation study of self-  
69 reported diet and PA measures in older adults (n = 1082; 50-74 years). The aim of our secondary analyses  
70 was to examine the associations between gold-standard measures of FFM (deuterium dilution), PA (tri-  
71 axial accelerometry), TDEE (doubly labelled water; DLW) and self-reported EI (with and without  
72 adjustment for under-reporting) in a sub-sample of data where relevant outcomes were available (n = 590).

73

## 74 **METHODS**

### 75 **Participants and Study Design**

76 The present paper was a secondary analysis of 590 participants from a total of 1082 participants enrolled  
77 in the IDATA Study (see **Table 1** for descriptive characteristics). The primary aim of the IDATA study

78 was to evaluate how well internet-based, self-report instruments measure EI and PA levels and their  
79 relationship with disease, and it was registered at [clinicaltrials.gov](http://clinicaltrials.gov) as: [NCT03268577](https://clinicaltrials.gov/ct2/show/study/NCT03268577)  
80 (<http://www.clinicaltrials.gov>). In the present analyses, only participants with valid measures of body  
81 composition (deuterium dilution), PA (tri-axial accelerometry), TDEE (DLW) and EI (24-hour recall) were  
82 included. A participant flow diagram for the main IDATA study can be found in Supplementary Materials  
83 Figure 1, while a flow diagram detailing the inclusion/exclusion of participants used in the present analyses  
84 can be found in Supplementary Materials Figure 2. Participants were aged between 50-74 years, English  
85 speaking, not following a weight loss diet, had internet access, and were free from mobility limitations and  
86 major medical conditions (history of renal failure, congestive heart failure, or other conditions involving  
87 disturbances in fluid balance). Participants enrolled in the IDATA study were randomly assigned to 1 of 4  
88 study groups to reduce seasonal variation in diet and PA and completed a 12-month assessment period  
89 (groups 1–4:  $n = 183, 192, 240,$  and  $460,$  respectively). Data collection was identical for each group except  
90 that in Groups 1 and 3 TDEE and PA were measured during Month One while in Groups 2 and 4 these were  
91 measured in Month Six (see **Table 2**). Anthropometric measures were taken during clinical laboratory visits  
92 at Months One, Six and Twelve in all participants, while total daily EI was estimated bi-monthly using  
93 online 24-hour dietary recalls. All participants provided written consent and the study was approved by the  
94 National Cancer Institute Special Studies Institutional Review Board. Individuals who completed the study  
95 received \$450. The present analyses were not part of the *a priori* outcomes of the IDATA study. Data were  
96 accessed through the Cancer Data Access System (<https://cdas.cancer.gov/idata/>) after project proposal  
97 approval by the National Cancer Institute (<https://cdas.cancer.gov/approved-projects/1916/>).

98 **Table 1 here**

99

100 **Total Daily Energy Expenditure**

101 Total daily energy expenditure was estimated over a 14-day period (month one for Groups 1 and 3, month  
102 six for Groups 2 and 4) using DLW as previously described (23). Following an overnight fast (>8hrs),  
103 participants provided a baseline urine sample and consumed orally a pre-prepared dose of  $^2\text{H}_2^{18}\text{O}$  based on



104 their body mass (2 g of 10 atom percent  $^{18}\text{O}$  labelled water and 0.12 g of 99.9 atom percent deuterium  
105 labelled water per kg of estimated total body water). After consumption, participants provided an hourly  
106 urine sample for four hours. One hour after dosing, an 8-ounce (240 mL) can of meal-replacement beverage  
107 was provided. Participants could drink an additional 7 ounces (210 mL) of liquid over the next 4 h, with  
108 liquid intakes recorded. Two final urine samples were collected 14 days after the initial dosing day. Total  
109 daily energy expenditure was calculated using the equation of Racette et al. (24) and the modified Weir  
110 equation, assuming a respiratory quotient of 0.86 for all participants. Urine samples were analysed at the  
111 University of Wisconsin's Isotope Ratio Mass Spectrometry Core by using the isotope measurement  
112 method described in the OPEN study (23).

113 **Table 2 here**

114

115 **Body Composition and Anthropometry**

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

125

126 **Physical Activity**

127 The measurement of PA, and its relationship to TDEE, have been described in detail elsewhere (27). Briefly,  
128 PA was measured using hip worn tri-axial accelerometers (ActiGraph GT3X) with participants asked to  
129 wear the device for seven consecutive days and only to remove it when showering, bathing, swimming and

130 immediately prior to bed at night. Two 7-day PA collection periods were conducted in the IDATA study,  
131 but the present analysis only used the 7-day period corresponding to the month in which the DLW  
132 measurement was taken (Month One for Groups 1 and 3; Month Six for Groups 2 and 4). Mean activity  
133 counts per days (CPM/D) were calculated from the vector magnitude of the X, Y and Z axes using data  
134 averaged over 60 second epochs. A minimum of 10 hours of wear time was needed to constitute a valid  
135 measurement day (27), with the Choi algorithm (28) used to estimate non-wear time from vector magnitude  
136 data using the ‘PhysicalActivity’ package in Rstudio version 1.4.1717. A minimum of 4 valid days were  
137 required to be included in the present analysis, with participants having on average 6 valid days of  
138 accelerometer data and a mean wear time of 14.8 hrs per day.

139

#### 140 **Total Daily Energy Intake**

141 Total daily EI was estimated in the IDATA study using six bi-monthly 24-hour dietary recalls during the  
142 12-month study period (see Table 2). In the present analysis, total daily EI was estimated from a single  
143 dietary recall performed  $\pm$  one month of PA and TDEE measurement ( $EI_{\text{single}}$ ), and the mean of the six  
144 recalls ( $EI_{\text{mean}}$ ) as the use multiple recalls has been shown to better reflect habitual food intake (29). For  
145  $EI_{\text{mean}}$ , participants completed an average of  $5.6 \pm 0.8$  dietary recalls. The ASA24, a web-based dietary  
146 assessment tool modelled on the USDA’s Automated Multiple-PASS Method for 24-hour dietary recalls  
147 (30), was used to estimate EI. Participants were asked via e-mail to complete six ASA24s, each  
148 unannounced and on a randomly assigned day, approximately every other month. If a participant did not  
149 complete the requested ASA24 within 24 hours of e-mail notification, a reminder e-mail was sent on a new  
150 randomly selected day. Participants were provided 3 attempts to complete each of the required 6 dietary  
151 recalls. Nutrient and food group intakes in the ASA24 were estimated by using the USDA’s Food and  
152 Nutrient Database for Dietary Studies, version 4.1; MyPyramid Equivalent Database, version 2.0; and the  
153 NHANES Dietary Supplement Database 2007–2008. The IDATA study also included 4-day food records  
154 and a food frequency questionnaire, but these were not closely aligned with PA or TDEE measurement and

155 the ASA24 has previously been shown to provide the best estimate of total daily EI relative to TDEE in  
 156 these data (31).

157

### 158 **Mis-Reporting of Total Daily Energy Intake**

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

161

162 •  $95\% \text{ CL} = 2 \times \text{sqrt}[(CV_{wEI}^2/d) + CV_{wEE}^2 - 2r \cdot (CV_{wEI}/d) \cdot CV_{wEE}]$

163

164 Where d is the number of days of diet assessment, r is the Pearson's correlation coefficient between DLW-  
 165 derived TDEE and  $EI_{\text{mean}}$ , the mean coefficient of EI variation ( $CV_{wEI}$ ) was assumed to be 23% and the  
 166 coefficient of variation for DLW energy expenditure ( $CV_{wEE}$ ) was assumed to be 8.2% based on the values  
 167 proposed by Black et al. (32). Acceptable reporters were defined as having an EI:TDEE ratio between 0.77-  
 168 1.23, under-reporters as having a ratio EI:TDEE <0.77, and over-reporters as an EI:TDEE ratio >1.23.

169

### 170 **Statistical Analysis**

171 Statistical analyses were performed using Rstudio version 1.4.1717 and data are reported as mean  $\pm$  SD.

172 Independent two sample Welch's t-tests were used to examine for differences between males and female.

173 Paired t-tests were used to examine for differences between  $EI_{\text{single}}$  and  $EI_{\text{mean}}$  and between EI and TDEE.

174 Bland and Altman plots were also used to compare the difference between  $EI_{\text{single}}$  or  $EI_{\text{mean}}$  and TDEE using

175 the 'blandr' package in Rstudio. Pearson's correlations were used to examine the associations between body

176 composition, PA and TDEE with  $EI_{\text{single}}$  or  $EI_{\text{mean}}$ . As age-related changes in FFM, PA and TDEE may

177 accelerate during later life (33, 34), moderation analyses using PROCESS for SPSS (version 3.2) (35) was

178 used to examine whether age moderated the associations between FFM or TDEE and EI, with Pearson's

179 correlations repeated in each separate age quintile (see Supplementary Materials Table 1 for descriptive

180 characteristics by age quintiles). Linear regression was used to examine for predictors of EI based on our

181 previous findings in young and middle aged adults (5-7). In Models 1-3  $EI_{single}$  was used as the dependent  
182 variable, with FM and FFM entered as independent variables in Model 1, FM, FFM and PA in Model 2,  
183 and FM, FFM, PA and TDEE in Model 3. The same models were repeated using  $EI_{mean}$  as the dependent  
184 variable (models 4-6), and following removal of participants classified as under-reporters (models 7-9).  
185 Given their known effects on FFM, TDEE and EI, sex and age were included in all regression models. As  
186 body weight was measured on three occasions during the study (months 1, 6 and 12; mean change =  $-0.22$   
187  $\pm 3.59$  kg), weight change was also initially added as a predictor of EI. However, weight change did not  
188 predict EI or influence the associations between the remaining predictors, and therefore was not included.  
189 Visual inspection of model residual Q-Q plots confirmed no serious violations of normality, while linearity  
190 was confirmed via visual inspection of residual plots and homoscedasticity via Scale-Location plot  
191 inspection. Multicollinearity was assessed using the variance inflation factor (VIF), which indicated that  
192 there was no instability in any of the models with VIF scores  $<6.43$  for all predictors included (36).  
193 Examination of Cook's Distance indicated the presence of 4 influential outliers in 1 or more of regression  
194 models 1-6 (Cook's Distance  $> 0.5$  and a standardised residual  $>4.0$ ). Therefore, these individuals were  
195 removed and regression analyses conducted in 586 individuals in these models. Their removal did not alter  
196 interpretation of model estimates or outcomes, but did result in a small increase in explained variance  
197 (increase in adj  $R^2$  between 0.6 to 1.5%). To account for differences in FM and FFM due to height,  
198 regression analyses were also repeated using the FM ( $FM/height^2$ ) and FFM ( $FFM/height^2$ ) indexes, but  
199 main outcomes again did not differ (see Supplementary Materials Table 2).

200

## 201 RESULTS

202 Participant descriptive characteristics can be found in Table 2. As would be expected, FFM was higher in  
203 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  
204 were less active than female ( $t_{(586.3)} = 3.1$ ,  $p = 0.002$ ), but TDEE was higher in males ( $t_{(550.1)} = 17.5$ ,  $p <$   
205  $0.001$ ). Total daily EI did not differ when estimated from a single 24-hour dietary recall ( $EI_{single}$ ) or based  
206 on the mean of six recalls ( $EI_{mean}$ ;  $9.3 \pm 587$  kcal/day;  $t_{(589)} = 0.4$ ,  $p = 0.699$ ). Both  $EI_{single}$  ( $t_{(578.9)} = 6.4$ ,  $p <$

0.001) and  $EI_{\text{mean}}$  ( $t_{(568.5)} = 10.2$ ,  $p < 0.001$ ) were higher in males than females. When EI was compared to TDEE,  $EI_{\text{single}}$  was  $-321 \pm 841$  kcal/day ( $t_{(589)} = 9.3$ ,  $p < 0.001$ ) lower than TDEE, while  $EI_{\text{mean}}$  was  $-312 \pm 622$  kcal/day lower ( $t_{(589)} = 12.2$ ,  $p < 0.001$ ). Limits of agreement between EI and TDEE were smaller with  $EI_{\text{mean}}$  (**Figure 1**), with the lower and upper limits of agreement for  $EI_{\text{single}}$   $-1327$  (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

$EI_{\text{single}}$  and  $EI_{\text{mean}}$  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  $EI_{\text{single}}$  ( $F_{(3, 586)} = 21.57$ ,  $R^2 = 0.10$ ,  $p < 0.001$ ) or  $EI_{\text{mean}}$  ( $F_{(3, 586)} = 50.69$ ,  $R^2 = 0.21$ ,  $p < 0.001$ ), with the strength of associations between FFM and  $EI_{\text{single}}$  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  $EI_{\text{mean}}$  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  $EI_{\text{single}}$  ( $F_{(3, 586)} = 23.96$ ,  $R^2 = 0.11$ ,  $p < 0.001$ ), with the strength of association with  $EI_{\text{single}}$  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  $EI_{\text{mean}}$  ( $F_{(3, 586)} = 44.74$ ,  $R^2 = 0.19$ ,  $p < 0.001$ ), although the associations between TDEE and  $EI_{\text{mean}}$  did become weaker across age quintile 1 ( $r = 0.52$ ;  $p < 0.001$ ), quintile 2 ( $r =$

233 0.41;  $p < 0.001$ ), quintile 3 ( $r = 0.42$ ;  $p < 0.001$ ), quintile 4 ( $r = 0.37$ ;  $p < 0.001$ ) and quintile 5 ( $r = 0.38$ ;  $p$   
 234  $< 0.001$ ).

235 **Figure 2 here**

236

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

239 To examine the relationships between body composition, PA, TDEE and  $EI_{single}$ , three linear regression  
 240 models were examined (**Table 3**). In Model 1 ( $F_{(4, 581)} = 16.15$ ,  $p < 0.001$ ; adj  $R^2 = 0.093$ ), FFM ( $\beta = 0.30$ ;  
 241  $p < 0.001$ ) and FM ( $\beta = -0.10$ ;  $p = 0.044$ ) predicted  $EI_{single}$ , but age and sex were not predictors. The addition  
 242 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  
 243 FFM ( $\beta = 0.33$ ;  $p < 0.001$ ) and PA ( $\beta = 0.10$ ;  $p = 0.018$ ), but not FM, independently predicting  $EI_{single}$ . When  
 244 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  
 245 TDEE ( $\beta = 0.15$ ;  $p = 0.022$ ) predicted  $EI_{single}$ . When these models were repeated using  $EI_{mean}$  as the  
 246 dependent variable (Models 4-6), FFM ( $\beta = 0.46$ ;  $p < 0.001$ ) and FM ( $\beta = -0.10$ ;  $p = 0.026$ ) were again  
 247 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,  
 248 when PA was added, FFM ( $\beta = 0.48$ ;  $p < 0.001$ ) and PA ( $\beta = 0.09$ ;  $p = 0.033$ ) predicted  $EI_{mean}$  (Model 5;  
 249  $F_{(4, 580)} = 36.23$ ,  $p < 0.001$ ; adj  $R^2 = 0.231$ ), but with the addition of TDEE (Model 6;  $F_{(6, 579)} = 30.99$ ,  $p <$   
 250  $0.001$ ; adj  $R^2 = 0.235$ ), only FFM ( $\beta = 0.37$ ;  $p < 0.001$ ) and TDEE ( $\beta = 0.12$ ;  $p = 0.049$ ) predicted  $EI_{mean}$ .

251

252 **Table 3 here**

253

254 **Mis-Reporting of Total Daily Energy Intake**

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

258 0.001) remaining independent predictors of  $EI_{\text{mean}}$  when included alongside age, sex, FM and PA ( $F_{(6, 378)} =$   
259 58.49,  $p < 0.001$ ;  $\text{adj } R^2 = 0.473$ ; Model 9).

260

## 261 **DISCUSSION**

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

272

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

274 In line with previous work in young and middle-aged adults (8-12), we demonstrate here that FFM and  
275 TDEE, but not FM, were positively associated with EI in this sample of older adults, suggesting that the  
276 amount of FFM and TDEE is proportional to daily EI in older adults. We have previously proposed that  
277 such findings reflect an underlying long-term or tonic drive to eat that ensures the energetic demands of  
278 key tissue-organs (e.g., FFM) and metabolic processes (e.g., RMR) are met through daily food intake (5-  
279 7). As an important determinant of RMR and TDEE, this positions FFM as a key feature of homeostatic  
280 appetite control that operates alongside adipose and gastro-intestinal satiety signals in the overall expression  
281 of appetite and food intake. It has been suggested that the lower levels of hunger and EI seen in older adults  
282 may reflect age-related changes in energy requirements subsequent to reductions in FFM, RMR and PA  
283 energy expenditure (37). While this implies some form of ‘coupling’ between the demand for energy arising

284 from the biological processes and behavioural activities of daily living and EI, there is currently little  
285 empirical evidence that TDEE or its main determinants influence appetite or food intake in older adults.  
286 Indeed, we are aware of one study in which direct associations between FFM and appetite and EI have been  
287 demonstrated in older adults, with Johnson et al. (38) reporting that the change in FFM (+1.2 kg) following  
288 12 weeks of resistance exercise and protein supplementation was associated with the change in EI (+119  
289 kcal) during an *ad libitum* test meal ( $r = 0.53$ ). Limited cross-sectional evidence also exists linking impaired  
290 appetite in older adults to reduced lean tissue mass and/or sarcopenia (39-42), but such studies are typically  
291 reliant on questionnaires (often with dichotomous yes/no questions) designed to quantify malnutrition (e.g.,  
292 SNAQ, MUST, MNA-SF) rather than objective measures of appetite or food intake. However, as age-  
293 related appetite impairment reflects multi-factorial biological, psycho-social, environmental factors, and  
294 disease states and associated treatment (1), longitudinal studies that track changes in body composition and  
295 energy expenditure alongside appetite and EI are needed to establish a causal role for FFM and TDEE in  
296 the control of appetite of older adults and its dysregulation with aging.

297  
298 In the present study PA was also found to predict EI, but its effect was modest and only explained 1-4% of  
299 the variance in EI when included alongside age, sex, FM and FFM. Further, when TDEE was added to these  
300 regression models, TDEE typically displaced PA as a predictor of EI. These findings, which are in  
301 agreement with our previous work in which activity energy expenditure predicted daily EI in free-living  
302 adults (accounting for 3% of the variance in total daily EI) (14), suggest that the energetic cost of PA may  
303 also influence EI via its contribution to TDEE, albeit more modestly than FFM or RMR. This modest  
304 contribution is perhaps not surprising given the smaller and more variable contribution of PA energy  
305 expenditure to TDEE as compared to FFM or RMR (43). In a recent publication using the present IDATA  
306 dataset examining Pontzer's hypothesis of constrained TDEE (44), a positive linear relationship was found  
307 between PA and TDEE across the entire cohort (27). It has previously been suggested that increasing PA  
308 would be a viable means of increasing appetite and EI in older adults, but the effect of exercise and/or PA  
309 on the mechanisms that control appetite in older adults is unclear (45).



310

**311 Differences in the Strength of the Associations with Increasing Age**

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

336

**337 Under-Reporting of Total Daily Energy Intake**

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

358

**359 Strengths and Limitations**

360 This study used a large sample of older adults to examine the associations between body composition, PA  
361 and TDEE with EI using gold standard measures of FFM, PA and TDEE. Findings that FFM and TDEE

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

383

## 384 **Conclusions**

385 Our findings provide evidence that FFM and TDEE are associated with EI in older adults, and consistent  
386 with previous findings in young adults, suggest that total daily EI is proportional to the amount of FFM and  
387 TDEE (but not FM) in older adults. These associations between FFM and TDEE with EI may reflect an

388 underlying drive to eat that influences daily food intake in older adults. While the associations between  
389 FFM or TDEE and EI were found to exist across all age quintiles, these associations weakened with  
390 increasing age and future research should examine the potential for a bi-directional relationship between  
391 FFM loss and appetite impairment with aging. When considered alongside existing understanding of age-  
392 related changes in post-prandial satiety signalling and gastric motility/emptying, such data would provide  
393 a stronger account of the physiological mechanisms that underlie the drive and inhibition of appetite in  
394 older adults and its dysregulation with aging.

395

#### 396 **ACKNOWLEDGMENTS**

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

400

401 Data described in the manuscript are publicly and freely available upon request via the National Cancer  
402 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;  $EI_{\text{single}}$ , total daily energy intake estimated from a single dietary 24-hour recall;  $EI_{\text{mean}}$ , 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  $\pm$  SD) for the whole sample and after removal of those classified as under-reporters based on the 95% confidence intervals between  $EI_{\text{mean}}$  and total daily energy expenditure.

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

N; number of participants, BMI; body mass index, TDEE; total daily energy expenditure, CPM/D; counts per minute per day,  $EI_{\text{single}}$ ; total daily energy intake estimated from a single 24-hour dietary recall,  $EI_{\text{mean}}$ , 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
<b>Groups One &amp; Three</b>												
<b>TDEE (DLW)</b>												
<b>Physical Activity</b>												
<b>Energy Intake</b>												
<b>Anthropometry</b>												
<b>Groups Two &amp; Four</b>												
<b>TDEE (DLW)</b>												
<b>Physical Activity</b>												
<b>Energy Intake</b>												
<b>Anthropometry</b>												

DLW; doubly labelled water, TDEE; total daily energy expenditure. Groups 1–4:  $n = 183, 192, 240,$  and  $460,$  respectively. Of note,  $EI_{\text{single}}$  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.



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	<b>-221.3</b>	<b>94.1</b>	<b>-0.20</b>	<b>0.019</b>	<b>-200.9</b>	<b>92.2</b>	<b>-0.17</b>	<b>0.029</b>	<b>-212.1</b>	<b>86.0</b>	<b>-0.18</b>	<b>0.015</b>
FM (kg)	<b>-6.8</b>	<b>3.1</b>	<b>-0.11</b>	<b>0.029</b>	-3.9	3.1	-0.07	0.202	-4.4	2.9	-0.07	0.131
FFM (kg)	<b>43.2</b>	<b>4.7</b>	<b>0.78</b>	<b>&lt;0.001</b>	<b>43.8</b>	<b>4.6</b>	<b>0.79</b>	<b>&lt;0.001</b>	<b>21.4</b>	<b>5.2</b>	<b>0.39</b>	<b>&lt;0.001</b>
PA (CPM/D)					<b>0.4</b>	<b>0.1</b>	<b>0.18</b>	<b>&lt;0.001</b>	0.1	0.1	0.05	0.240
TDEE (kcal/day)									<b>0.6</b>	<b>0.1</b>	<b>0.49</b>	<b>&lt;0.001</b>

FM; fat mass, FFM; fat-free mass, PA; physical activity, TDEE; total daily energy expenditure, CPM/D; counts per minute per day, EI<sub>single</sub>; total daily energy intake estimated from a single 24-hour dietary recall, EI<sub>mean</sub>, 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<sub>single</sub> 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<sub>mean</sub> 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.