See corresponding editorial on page 1579.

Physical activity and fat-free mass during growth and in later life

Klaas R Westerterp,[1] Yosuke Yamada,[2,3] Hiroyuki Sagayama,[4] Philip N Ainslie,[5] Lene F Andersen,[6] Liam J Anderson,[5,7] Lenore Arab,[8] Issaad Baddou,[9] Kweku Bedu-Addo,[10] Ellen E Blaak,[11] Stephane Blanc,[12,13] Alberto G Bonomi,[14] Carlijn VC Bouten,[15] Pascal Bovet,[16] Maciej S Buchowski,[17] Nancy F Butte,[18] Stefan GJA Camps,[11] Graeme L Close,[5] Jamie A Cooper,[12] Sai K Das,[19] Richard Cooper,[20] Lara R Dugas,[20] Ulf Ekelund,[21] Sonja Entringer,[22,23] Terrence Forrester,[24] Barry W Fudge,[25] Annelies H Goris,[11] Michael Gurven,[26] Catherine Hambly,[27] Asmaa El Hamdouchi,[9] Marije B Hoos,[11] Sumei Hu,[28] Noorjehan Joonas,[29] Annemiek M Joosen,[11] Peter Katzmarzyk,[30] Kitty P Kempen,[11] Misaka Kimura,[2] William E Kraus,[31] Robert F Kushner,[32] Estelle V Lambert,[33] William R Leonard,[34] Nader Lessan,[35] Corby K Martin,[30] Anine C Medin,[6,36] Erwin P Meijer,[11] James C Morehen,[5,37] James P Morton,[5] Marian L Neuhouser,[38] Theresa A Nicklas,[18] Robert M Ojiambo,[39,40] Kirsi H Pietiläinen,[41] Yannis P Pitsiladis,[42] Jacob Plange-Rhule,[10] Guy Plasqui,[43] Ross L Prentice,[38] Roberto A Rabinovich,[44] Susan B Racette,[45] David A Raichlen,[46] Eric Ravussin,[30] Rebecca M Reynolds,[47] Susan B Roberts,[19] Albertine J Schuit,[48] Anders M Sjödin,[49] Eric Stice,[50] Samuel S Urlacher,[51] Giulio Valenti,[11] Ludo M Van Etten,[11] Edgar A Van Mil,[52] Jonathan CK Wells,[53] George Wilson,[5] Brian M Wood,[54,55] Jack Yanovski,[56] Tsukasa Yoshida,[4] Xueying Zhang,[27,28] Alexia J Murphy-Alford,[57] Cornelia U Loechl,[57] Amy H Luke,[58] Herman Pontzer,[59,60] Jennifer Rood,[30] Dale A Schoeller,[61] William W Wong,[18] and John R Speakman,[27,28,62,63] the International Atomic Energy Agency Doubly Labeled Water database group

[1]School of Nutrition and Translational Research in Metabolism, University of Maastricht, Maastricht, The Netherlands; [2]National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health and Nutrition, Tokyo, Japan; [3]Institute for Active Health, Kyoto University of Advanced Science, Kyoto, Japan; [4]Faculty of Health and Sport Sciences, University of Tsukuba, Tsukuba, Japan; [5]Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, United Kingdom; [6]Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway; [7]Crewe Alexandra Football Club, Crewe, United Kingdom; [8]David Geffen School of Medicine, University of California, Los Angeles, CA, USA; [9]Unité Mixte de Recherche en Nutrition et Alimentation, CNESTEN–Université Ibn Tofail URAC39, Regional Designated Center of Nutrition Associated with African Regional Agreement for Research/International Atomic Energy Agency, Rabat, Morocco; [10]Department of Physiology, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; [11]Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, Netherlands; [12]Nutritional Sciences, University of Wisconsin, Madison, WI, USA; [13]Institut Pluridisciplinaire Hubert Curien. CNRS Université de Strasbourg, UMR7178, Strasbourg, France; [14]Phillips Research, Eindhoven, The Netherlands; [15]Department of Biomedical Engineering and Institute for Complex Molecular Systems, Eindhoven University of Technology, Eindhoven, The Netherlands; [16]University Center for Primary Care and Public Health (Unisanté), Lausanne, Switzerland; [17]Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, Vanderbilt University, Nashville, TN, USA; [18]Department of Pediatrics, Baylor College of Medicine, USDA/Agricultural Research Service Children's Nutrition Research Center, Houston, TX, USA; [19]Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA, USA; [20]Department of Public Health Sciences, Parkinson School of Health Sciences and Public Health, Loyola University, Maywood, IL, USA; [21]Department of Sport Medicine, Norwegian School of Sport Sciences, Oslo, Norway; [22]Institute of Medical Psychology, Charité—Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health (BIH), Berlin, Germany; [23]Department of Pediatrics, University of California Irvine, Irvine, CA, USA; [24]Solutions for Developing Countries, University of the West Indies, Mona, Kingston, Jamaica; [25]Institute of Biomedical and Life Sciences, University of Glasgow, Glasgow, United Kingdom; [26]Department of Anthropology, University of California Santa Barbara, Santa Barbara, CA, USA; [27]Institute of Biological and Environmental Sciences, University of Aberdeen, Aberdeen, United Kingdom; [28]State Key Laboratory of Molecular Developmental Biology, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing, China; [29]Central Health Laboratory, Ministry of Health and Wellness, Port Louis, Mauritius; [30]Pennington Biomedical Research Center, Baton Rouge, LA, USA; [31]Department of Medicine, Duke University, Durham, NC, USA; [32]Department of Medicine, Northwestern University, Chicago, IL, USA; [33]Research Unit for Exercise Science and Sports Medicine, University of Cape Town, Cape Town, South Africa; [34]Department of Anthropology, Northwestern University, Evanston, IL, USA; [35]Imperial College London Diabetes Centre, Imperial College London, London, United Kingdom; [36]Department of Nutrition and Public Health, Faculty of Health and Sport Sciences, University of Agder, Kristiansand, Norway; [37]The FA Group, Burton-Upon-Trent, United Kingdom; [38]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center and School of Public Health, University of Washington, Seattle, WA, USA; [39]Department of Medical Physiology, Moi University, Eldoret, Kenya; [40]Department of Biomedical Sciences, University of Global Health Equity, Butaro, Rwanda; [41]Helsinki University Central Hospital, Helsinki, Finland; [42]Collaborating Centre of Sports Medicine, University of Brighton, Eastbourne, United Kingdom; [43]Department of Nutrition and Movement Sciences, Maastricht University, Maastricht, The Netherlands; [44]Department of Respiratory Medicine, University of Edinburgh, Edinburgh, United Kingdom; [45]Program in Physical Therapy

and Department of Medicine, Washington University School of Medicine, St Louis, MO, USA; [46]Biological Sciences and Anthropology, University of Southern California, Los Angeles, CA, USA; [47]Centre for Cardiovascular Sciences, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom; [48]School of Social and Behavioural

Am J Clin Nutr 2021;114:1583–1589. Printed in USA. 1583 Sciences, University of Tilburg, Tilburg, The Netherlands; [49]Department of Nutrition, Exercise and Sports, Copenhagen University, Copenhagen, Denmark; [50]Department of Psychiatry, Stanford University, Stanford, CA, USA; [51]Department of Anthropology, Baylor University, Waco, TX, USA; [52]Faculty of Health, Medicine and Life Sciences, and Faculty of Science and Engineering, Maastricht University, Maastricht, The Netherlands; [53]Population, Policy and Practice Research andTeaching Department, UCLGreat OrmondStreetInstitute ofChildHealth, London,United Kingdom; [54]Departmentof Antropology,University of California Los Angeles, Los Angeles, CA, USA; [55]Department of Human Behavior, Ecology, and Culture, Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany; [56]Section on Growth and Obesity, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, Bethesda, MD, USA; [57]Nutritional and Health-Related Environmental Studies Section, Division of Human Health, International Atomic Energy Agency, Vienna, Austria; [58]Division of Epidemiology, Department of Public Health Sciences, Loyola University School of Medicine, Maywood, IL, USA; [59]Evolutionary Anthropology, Duke University, Durham, NC, USA; [60]Duke Global Health Institute, Duke University, Durham, NC, USA; [61]Biotech Center and Nutritional Sciences, University of Wisconsin, Madison, WI, USA; [62]Center for Energy Metabolism and Reproduction, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China; and [63]CAS Center of Excellence in Animal Evolution and Genetics, Kunming, China

ABSTRACT

Background: Physical activity may be a way to increase and maintain fat-free mass (FFM) in later life, similar to the prevention of fractures by increasing peak bone mass.

Objectives: A study is presented of the association between FFM and physical activity in relation to age.

Methods: In a cross-sectional study, FFM was analyzed in relation to physical activity in a large participant group as compiled in the International Atomic Energy Agency Doubly Labeled Water database. The database included 2000 participants, age 3–96 y, with measurements of total energy expenditure (TEE) and resting energy expenditure (REE) to allow calculation of physical activity level (PAL = TEE/REE), and calculation of FFM from isotope dilution.

Results: PAL was a main determinant of body composition at all ages. Models with age, fat mass (FM), and PAL explained 76% and 85% of the variation in FFM in females and males < 18 y old, and 32% and 47% of the variation in FFM in females and males ≥ 18 y old, respectively. In participants < 18 y old, mean FM-adjusted FFM was 1.7 kg (95% CI: 0.1, 3.2 kg) and 3.4 kg (95% CI: 1.0, 5.6 kg) higher in a very active participant with PAL = 2.0 than in a sedentary participant with PAL = 1.5, for females and males, respectively. At age 18 y, height and FM–adjusted FFM was 3.6 kg (95% CI: 2.8, 4.4 kg) and 4.4 kg (95% CI: 3.2, 5.7 kg) higher, and at age 80 y 0.7 kg (95% CI: −0.2, 1.7 kg) and 1.0 kg (95% CI: −0.1, 2.1 kg) higher, in a participant with PAL = 2.0 than in a participant with PAL = 1.5, for females and males, respectively.

Conclusions: If these associations are causal, they suggest physical activity is a major determinant of body composition as reflected in peak FFM, and that a physically active lifestyle can only partly protect against loss of FFM in aging adults. *Am J Clin Nutr* 2021;114:1583–1589.

Keywords: physical activity level, age, energy expenditure, body composition, doubly labeled water

Supported by US National Science Foundation grant BCS-1824466 (to HP). The funders played no role in the content of this article.

JP-R is deceased.

Address correspondence to KRW (e-mail: k.westerterp@maastrichtuniversity.nl) or JRS (e-mail: j.speakman@abdn.ac.uk) and AHL, HP, JR, HS, DAS, YY, and WWW as members of the database management group and additional corresponding authors.

Abbreviationsused:FFM,fat-freemass;FFMI,fat-freemassindex;FM,fat mass; FMI, fat mass index; PAL, physical activity level; REE, resting energy expenditure; TEE, total energy expenditure.

Received March 30, 2021. Accepted for publication July 14, 2021.

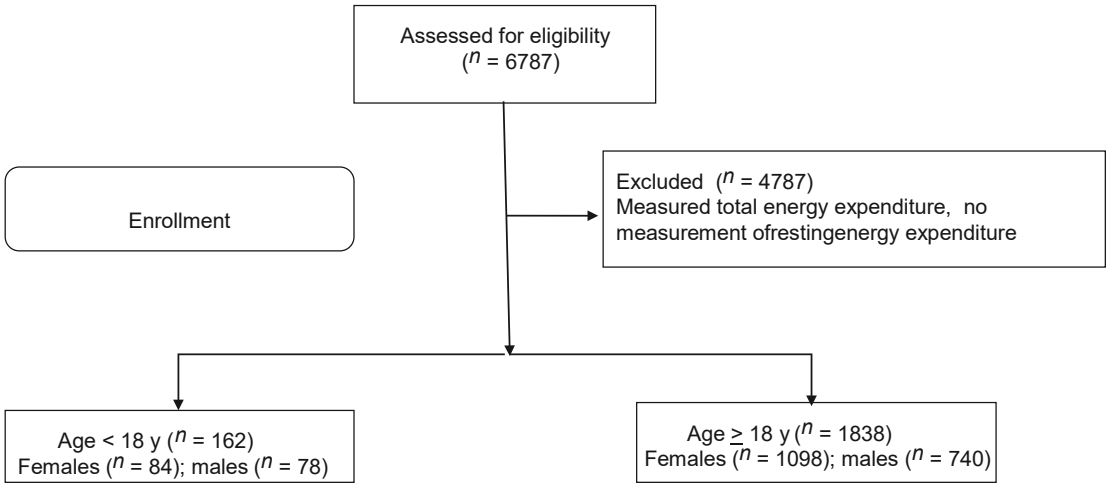
FirstpublishedonlineSeptember3,2021;doi:https://doi.org/10.1093/ajcn/nqab260.

Introduction

Physical activity provides a variety of health benefits. Physically active individuals sleep better and function better (1). In addition, physical activity can be an effective lifestyle behavior to maximize fat-free mass (FFM), as a proxy for muscle mass, during growth. Youth physical activity is positively associated withbonemassaccrualandbonestructure(2,3).Physicalactivity may be a way to increase and maintain FFM to prevent sarcopenia in later life, similar to the prevention of fractures by increasing peak bone mass (4–6).

Skeletal muscle accounts for about half of FFM. Muscle mass and bone mass are closely related throughout life, and FFM is the strongest determinant of whole-body bone mineral content. Modeling and remodeling processes that regulate bone strength potentially explain these relations, depending on the forces acting on the bones (7, 8). Physical activity positively affects FFM accretion from birth onwards (9). Physical activity during adolescence has been associated with greater FFM in both sexes (10). Habitual physical activity has been shown to have a significant independent effect on the growth of FFM during adolescence (11). These results support recommendations for sustained physical activity participation during the growing years (12).

FFM peaks in early adulthood (13). A cross-sectional analysis of a large multiethnic sample, ranging in age from 18 to 110 y, resulted in a quadratic model for FFM in relation to age with a peak FFM at similar ages for Caucasians, African Americans, Hispanics, and Asians. The estimated turning point, where growth ended and FFM started to decline, was in the mid-40s for females and mid-20s for males (13). Physical activity is likely to have a role in preventing FFM loss at later ages. A cross-sectional study showed that higher physical activity was associated with higher FFM in participants aged 60–64 y (14). A longitudinal study in participants aged 65–84 y showed that greater physical activity retained a greater FFM over 5 y of observation (15). On the other hand, a cross-sectional study in



529 participants aged 18–96 y suggested that greater physical activity was not
associated with higher FFM (16). Two longitudinal studies, the first in 904 participants aged 67–84 y and the second in 302 participants aged 70–82 y, also showed that changes in FFM over 5 y were not associated with physical activity level (PAL), when controlled for potential confounding variables (17, 18). Thus, there is still controversy on the relation between physical activity and FFM at later ages.

Here, the focus is on physical activity and FFM accrual during early and later life. A cross-sectional analysis was performed in a large participant group, deriving physical activity from doubly labeled water–measured energy expenditure. Thus, physical activity was quantified with a criterion measure (19).

FIGURE1 Participant flowchart.

Methods

The analysis included daily total energy expenditure (TEE) measurements as compiled in the International Atomic Energy Agency Doubly Labeled Water database (established to pool doubly labeled water data across multiple studies), version 3.1.2 (20). All data were recalculated with the same standard methodology for human doubly labeled water studies as published recently (21). The analysis was restricted to TEE measures accompanied by measurements of resting energy expenditure (REE), to allow calculation of PAL (TEE/REE). REE was measured under postabsorptive, thermoneutral, and resting conditions with a ventilated hood, or during an early morning resting interval, directly after waking up and before having breakfast, in a respiration chamber.

The database included 2000 participants (1182 females and 818 males) with measurements on TEE and REE to allow calculation of PAL (**Figure 1**). The age range of the participants was 3–96 y. The data analysis did not include participants with muscle wasting or participants with diseases affecting REE. All TEE measurements were performed under habitual daily life conditions, neutral energy balance, and before any study intervention. FFMwasderivedfromtotalbodywaterasmeasured with isotope dilution, a method directly derived from carcass analysis and thus 1 of the 2 single-indirect methods for body composition (22).

Associations between physical activity and FFM can be confounded by fat mass (FM) because gains or losses in fat typically lead to respective gains or losses in FFM (23). Changes in body weight and body composition are primarily a function of energy balance. Consequently, changes in FM and FFM are not independent (24). Energy balance–related body mass changes are generally assumed to consist of 75% as FM and 25% as FFM, which is known as the "quarter FFM" rule (25). Refinements of the quarter FFM rule were developed for specific situations like diet-induced weight change in extremely lean participants or participants with obesity (26, 27). Whatever rule applies for the relation between energy balance–induced changes in FM and FFM, FM should be included as an independent variable in an analysis on physical activity and FFM.

Data analysis was performed separately for participants < 18 y old and for participants ≥ 18 y old. For participants < 18 y old, the relation between FFM and PAL was assessed in a multiple regression model accounting for FM and age. To allow body composition comparisons between participants ≥ 18 y old, FFM and FM were expressed as indexes, the fatfree mass index (FFMI) and fat mass index (FMI), respectively, where FFMI = FFM/height^2 and FMI = FM/height^2 (FFM and FM in kg and height in m). In this way we corrected for differences in height, in analogy with the BMI of Quetelet: BMI = FFMI + FMI (28). Unfortunately, the index fails to adjust for height differences in participants during growth (29). Thus, data analysis was performed separately for participants < 18 y old, using unadjusted FFM and FM as measures for body composition. Models were generated separately for females and males. In participants ≥ 18 y old, 4 models were applied in a top-down procedure, with FFMI as the outcome variable:

- Model 1: age, FMI, PAL.
- Model 2: age, FMI, PAL, age^2.
- Model 3: age, FMI, PAL, age^2, age*PAL.
- Model 4: age, FMI, PAL, age^2, age*PAL, age^2*PAL.

Because the linearity assumption for age was violated, a quadratic term (age^2) needed to be included. The model explaining most variation in FFM from age-, FM-, and PALdifferences between participants was model 3. For females, model 3 was better than model 2, and model 4 was not better than model 3. For males, model 3 was as good as model 2, and model

4 was not better than model 3. Thus, model 3 was chosen for both sexes. Model 3 was checked for (multi)collinearity after centering for age, resulting in the same model fit and in condition indexes <30 (18.2 for females, 16.6 for males), indicating there was no collinearity problem.

Results

FFM was highest, around age 30 y, in females and males (**Figure 2**). The mean of peak FFM was 47 kg in females and 60 kg in males. Females showed a higher mean FM than males already at early ages. Mean PAL was similar in females and males at all ages (**Table 1**). The typical mean PAL value was ~1.5 in the youngest (age < 10 y) and oldest (age > 80 y) participants (Figure 2). At adult age, from 18 to 80 y, PAL values generally ranged between a minimum of 1.1 and a maximum

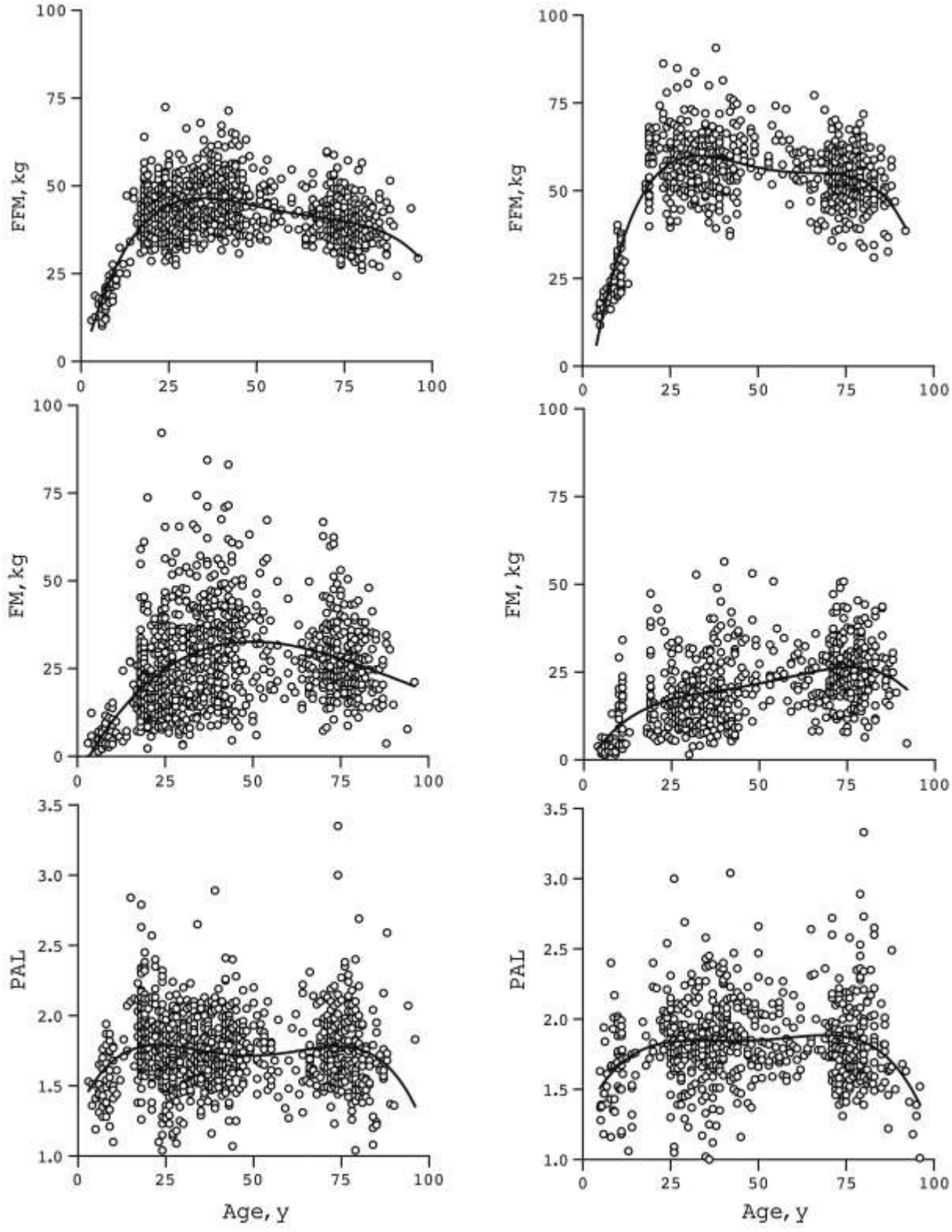


FIGURE 2 FFM, FM, and PAL, plotted as a function of age. Values for 2000 participants—1182 females (left) and 818 males (right)—with a 4th-order polynomial curve fit. FFM, fat-free mass; FM, fat mass; PAL, physical activity level.

TABLE1 Participant characteristics[1]

Characteristics	Females	Males
<18 y old *n*		
	84	78
Fat-free mass, kg	26.7 ± 10.9	26.9 ± 10.2
Fat mass, kg	10.8 ± 10.4	9.2 ± 7.7
PAL	1.61 ± 0.30	1.62 ± 0.29
≥18 y old *n*		
	1098	740
Fat-free mass index, kg/m^2	16.2 ± 2.3	18.5 ± 2.2
Fat mass index, kg/m^2	10.3 ± 4.9	7.4 ± 3.6
PAL	1.71 ± 0.26	1.78 ± 0.30

[1]Values are mean ± SD unless otherwise indicated. PAL, physical activity level.

of 2.5 with a mean ± SD value of 1.71 ± 0.26 for females and 1.78 ± 0.30 for males.

In participants < 18 y old (n= 162), FFM was significantly higher in individuals with an older age, higher FM, and higher PAL (**Table 2**):

- Females, FFM (kg) =−1.53 + 1.90 Age (y) + 0.21 FM (kg) + 3.34 PAL, R^2 = 0.85;
- Males, FFM (kg) =−7.42 + 2.00 Age (y) + 0.39 FM (kg) + 6.90 PAL, R^2 = 0.76.

Thus,meanFM-adjustedFFMwas1.7kg(95%CI:0.1,3.2kg) and 3.4 kg (95% CI: 1.0, 5.6 kg) higher in a very active participant with PAL = 2.0 than in a sedentary participant with PAL = 1.5, for females and males, respectively.

In participants ≥ 18 y old (n= 1838), FFMI was significantly higher in participants with a higher FMI and PAL for both sexes (**Table 3**):

- Females, FFMI (kg/m^2) = 7.15 + 0.094 Age (y) − 0.001 Age^2 (y) + 0.312 FMI (kg/m^2) + 3.214 PAL − 0.033 Age*PAL (y), R^2 = 0.47;
- Males, FFMI (kg/m^2) = 9.084 + 0.141 Age (y) − 0.001 Age^2 (y) + 0.308 FMI (kg/m^2) + 3.557 PAL − 0.036 Age*PAL (y), R^2 = 0.32.

At age 18 y, mean FMI-adjusted FFMI was 1.3 kg/m^2 (95% CI: 1.0, 1.6 kg/m^2) and 1.4 kg/m^2 (95% CI: 1.0, 1.8 kg/m^2) higher in a very active participant with PAL = 2.0 than in a sedentary participant with PAL = 1.5, for females and males, respectively. The differences in FFMI imply, for a typical female with height 1.65 m and male with height 1.75 m, a mean FM-adjusted FFM difference of 3.6 kg (95% CI: 2.8, 4.4 kg) and 4.4 kg (95% CI: 3.2, 5.7 kg), respectively. The positive association between

TABLE2 Sources of variation in FFM in participants <18 y old[1]

	Unstandardized coefficient (B)	95% CI for B
Females		
(constant)	[redacted]	[redacted]
Age		
FM	0.21	0.10, 0.31
PAL	3.34	0.21, 6.47
Males		
(constant)	[redacted]	[redacted]
Age		
FM	0.39	0.22, 0.57
PAL	6.90	2.66, 11.15

TABLE3 Sources of variation in FFMI in participants ≥ 18 y old[1]

	Unstandardized coefficient (B)	95% CI for B	*P*
Females			
(constant)	7.150	5.466, 8.838	<0.001
Age	0.094	0.049, 0.140	<0.001
FMI	0.312	0.290, 0.334	<0.001
PAL	[redacted]3.214	[redacted]2.379, 4.050	<0.001
Age^2			<0.001
Age*PAL			<0.001
Males			
(constant)	9.084	6.674, 11.494	<0.001
Age	0.141	0.080, 0.201	<0.001
FMI	0.308	0.267, 0.349	<0.001
PAL	3.557	2.442, 4.671	<0.001
Age^2	[redacted]	[redacted]	<0.001
Age*PAL			<0.001

[1]Values are coefficients and *P* values from a multiple regression model of FFMI (kg/m^2) as a function of age (y), FMI (kg/m^2), PAL, and interactions with age (y), in females (n = 1098, R^2= 0.47) and males (n = 740, R^2 = 0.32). FFMI, fat-free mass index; FMI, fat mass index; PAL, physical activity level.

[1] Values are coefficients and *P* values from a multiple regression model of FFM (kg) as a function of age (y), FM (kg), and PAL, in females (n = 84, R^2 = 0.85) and males (n = 78, R^2 = 0.76). FFM, fat-free mass; FM, fat mass; PAL, physical activity level.

FMIadjusted FFMI and PAL was smaller the older the participant (Table 3). Thus, at age 80 y, the differences in FFM between a sedentary and very active female and male were 0.7 kg (95% CI: −0.2, 1.7 kg) and 1.0 kg (95% CI: −0.1, 2.1 kg), respectively.

Participants with a higher FM had a higher FFM. The mean of the coefficient was 0.21 and 0.39 kg FFM/kg FM, or 17% and 39% FFM/kg body mass, in females and males < 18 y old, respectively. At later ages (>18 y old), the mean of the coefficient was 0.312 and 0.308 kg FFM/kg FM in females and males, respectively, or 24% FFM/kg body mass.

Discussion

The data showed that physically active participants have higher FM-adjusted FFM already during growth under age 18 y. Thus, physical activity is a major determinant of body composition as reflected in FFM in this cross-sectional analysis. However, older age counteracted the positive association of physical activity with FFM. Peak FFM was observed around age 30 y, in females and in males (Figure 2).

Age of unadjusted peak FFM is clearly higher than age of peak bone mass, in females at 19–20 y and in males at 20–24 y, independently of race (5). The higher age for unadjusted peak FFM than for peak bone mass is probably explained by FMassociated FFM. FM was highest in females around age 50 y and in males around age 75 y (Figure 2). Thus, FM-associated FFM dominated the decrease in physical activity–associated FFM in participants with a higher FM.

A previous study found the age of unadjusted peak FFM to be in the mid-40s for females and mid-20s for males (13). In the current study, peak FFM was at ~30 y old for both males and females, a difference possibly explained by differences in FM and thus in FM-associated FFM between the populations of study.

In adults, larger FFM in participants with a larger FM follows the quarter FFM rule (25). On average, 24% of the higher body mass was FFM. Factors confounding the quarter FFM rule, including an extreme imbalance between energy intake and energy expenditure and effects of differences in physical activity, were excluded in the model as presented. All participants were observed under neutral conditions of energy balance, and measured PAL was included in the model as an independent variable. Unfortunately, the quarter FFM rule still lacks a mechanistic explanation (27).

The controversy on FFM maintenance through physical activity at later age seems to be at least partly explained with inclusion of differences in FM between participants, in the model as presented. FFM adjusted for differences in FM was significantly higher in participants with a higher PAL, for females and males at younger age. The mean difference of 3.6 kg (95% CI: 2.8, 4.4 kg) and 4.4 kg (95% CI: 3.2, 5.7 kg) FFM at age 18 y and 0.7 kg (95% CI: −0.2, 1.7 kg) and 1.0 kg (95% CI: −0.1, 2.1) FFM at age 80 y, as calculated from the model presented, between a female and male with PAL = 1.5 and 2.0, respectively, is in line with an earlier cross-sectional analysis. Manini et al. (18) observed (mean ± SD) 2.0 ± 1.2 kg and 2.9 ± 1.3 kg greater FFM in older females and males, respectively, in participants in the first than in those in the third tertile of doubly labeled water– assessed activity energy expenditure. Differences in FM between participants in the first and third tertiles of activity energy expenditure were nonsignificant. However, despite a greater FFM in participants with a higher PAL, the age-related decline in FFM might not be prevented by a higher PAL.

In a 5-y follow-up of the participants 70–82 y old observed by Manini et al. (18), changes in physical activity did not affect the age-related change in body composition.

The average difference between peak FFM and FFM at age 80 y, an age interval where PAL remained the same, was −8 kg (Figure 2). The 8-kg difference between peak-FFM and FFM at age 80 y is similar to an earlier identical cross-sectional comparison resulting in −7.5 kg and −8.8 kg difference for females and males, respectively (30, 31). The mean difference in FM-adjusted FFM between a sedentary and a very active participant over the same age interval was between 3 and 4 kg. At older age, despite a greater routine physical activity, the inverse association of age*PAL counteracts the positive association of PAL with FFM.

Although aerobic exercise does not completely prevent the lower FFM in aging participants, resistance exercise may be more helpful (32). However, although resistance exercise elicited an ~1-kg increase in FFM among older adults, this is modest compared with the differences with healthy young adults and with the 8-kg difference aforementioned (33). Exercise training in adults at older age has little or no effect on muscle mass but is important for physical fitness and performance (34). Physical activity and exercise training increase functional capacity, allowing individuals to maintain their independence with increasing age and participate in activities associated with daily living (35).

One major cause of muscle mass loss with aging appears to be the alteration in hormonal activity involved in muscle regeneration and protein synthesis (36). Hormone replacement therapy in women is shown to diminish age-associated muscle loss and to raise the synthesis rate in skeletal muscle after exercise training (37). Thus, age-associated hormonal activity is one explanation for the age-associated interaction between physical activity and FFM.

From a longitudinal point of view, physical activity during growth may provide lifelong benefits by reaching higher peak FFM, as shown for physical activity and lifelong bone health (38, 39). Development of FFM and bone mass may be coordinated (40). The growth phase is a window of opportunity for achieving higher peak FFM to maximize bone mass, through a physically active lifestyle (41). If longitudinally confirmed, early-life physical activity may contribute to prevention of disease in old age (42).

Thestudyhasseveralstrengths.
Itwasconductedinalargeparticipant group (i.e., 2000 participants) covering early to late life, obtaining physical activity from doubly labeled water–measured energy expenditure and FFM from total body water as measured with isotope dilution, both considered gold-standard methods. An obvious limitation is the observational design. In addition, the use of the 2-compartment model of body composition cannot discern the differencein

changesofseparate componentsofFFM, including muscle mass and FM-associated FFM.

In conclusion, physically active participants show higher FMadjusted FFM, especially after growth at age 18 y. Thus, physical activity seems to be a major determinant of body composition as reflected in peak FFM. Older age counteracts the positive association of physical activity with FFM.

The doubly labeled water database, which can be found at https://doubly-labelled-water-database.iaea.org/home or https://www.dlwdatabase.org/, is generously supported by the International Atomic Energy Agency (IAEA), Taiyo Nippon Sanso, and SERCON. We are grateful to these companies for their support and especially to Takashi Oono for his tremendous efforts at fundraising on our behalf. The IAEA Doubly Labeled Water database group authorship contains the names of people whose data were contributed into the IAEA DLW database by the analysis laboratory but they later could not be traced, or they did not respond to emails to assent to inclusion among the authorship. The list also includes some researchers who did not assent to inclusion among the main authorship because they felt their contribution was not sufficient to merit authorship: Stefan Branth, University of Uppsala, Uppsala, Sweden; Lisa H Colbert, Kinesiology, University of Wisconsin, Madison, WI, USA; Niels C De Bruin, Erasmus University, Rotterdam, Netherlands; Alice E Dutman, TNO Quality of Life, Zeist, Netherlands; Sölve Elmståhl, Lund University, Lund, Sweden; Mikael Fogelholm, Department of Food and Nutrition, Helsinki, Finland; Tamara Harris, NIH, Bethesda, MD, USA; Rik Heijligenberg, Academic Medical Center of Amsterdam
University,Amsterdam,Netherlands;HansUJorgensen,BispebjergHospital, Copenhagen, Denmark; Christel L Larsson and Elisabet M Rothenberg, University of Gothenburg, Gothenburg, Sweden; Margaret McCloskey, Royal Belfast Hospital for Sick Children, Belfast, United Kingdom; Gerwin A Meijer, Daphne L Pannemans, Sabine Schulz, Rita Van den BergEmons, Wim G Van Gemert, Wilhelmine W Verboeket-van de Venne, and Jeanine A Verbunt, Maastricht University, Maastricht, Netherlands; Renaat M Philippaerts, Katholieke University Leuven, Leuven, Belgium; Amy Subar, Epidemiology and Genomics, Division of Cancer Control, NIH, Bethesda, MD, USA; Minna Tanskanen, University of Jyväskilä, Jyväskilä, Finland; Ricardo Uauy, Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago, Chile; and Erica J Velthuis-te Wierik, TNO Nutrition and Food Research Institute, Zeist, Netherlands.

The authors' responsibilities were as follows—KRW, YY, HS, AHL, HP, JR, DAS, WWW, and JRS: conceived the study; KRW: performed the data analysis and wrote the first draft; YY, HS, AHL, HP, JR, DAS, WWW, and JRS: commented on the manuscript; and all authors: contributed data to the study and read and approved the final manuscript. The authors report no conflicts of interest.

Data availability

Data All data used in these analyses are freely available via the International Atomic Energy Agency Doubly Labeled Water database (https://www.dlwdatabase.org/).

References

1. 2018 Physical Activity Guidelines Advisory Committee. 2018 Physical ActivityGuidelinesAdvisoryCommitteeScientificReport.Washington (DC): US Department of Health and Human Services; 2018.
2. Janz KF, Gilmore JM, Burns TL, Levy SM, Torner JC, WillingMC, Marshall TA. Physical activity augments bone mineral accrual in young children: the Iowa Bone Development study. J Pediatr 2006;148(6):793–9.
3. Janz KF, Letuchy EM, Eichenberger Gilmore JM, Burns TL, TomerJC, Willing MC, Levy SM. Early physical activity provides sustained bone health benefits later in childhood. Med Sci Sports Exerc 2010;42(6):1072–8.
4. Min S-K, Oh T, Kim SH, Cho J, Chung HY, Park D-H, Kim C-S.Position statement: exercise guidelines to increase peak bone mass in adolescents. J Bone Metab 2019;26:225–39.
5. Xue S, Kemal O, Lu M, Lix LM, Leslie WD, Yang S. Age atattainment of peak bone mineral density and its associated factors: the National Health and Nutrition Examination Survey 2005–2014. Bone 2020;131:1151–63.
6. Westerterp KR. Changes in physical activity over the lifespan: impacton body composition and sarcopenic obesity. Obes Rev 2018;19(Suppl 1):8–13.
7. Doyle F, Brown J, Lachance C. Relation between bone mass and muscleweight. Lancet 1970;295:391–3.
8. Vincente-Rodriguez G, Ara I, Perez-Gomez J, Dorado C, Calbet JAL.Muscular development and physical activity as major determinants of femoral bone mass acquisition during growth. Br J Sports Med 2005;39:611–16.
9. McGee M, Unger S, Hamilton J, Birken CS, Pausova Z, Vanderloo LM,Bando N, O'Connor DL. Lean mass accretion in children born very low birth weight is significantly associated with estimated changes from sedentary time to light physical activity. Pediatr Obes 2020;15:e12610.
10. Ramires VV, Dumith SC, Wehrmeister FC, Hallal PC, Menezes AMB,Gonçalves H. Physical activity throughout adolescence and body composition at 18 years: 1993 Pelotas (Brazil) birth cohort study. Int J Behav Nutr Phys Act 2016;13:105.
11. Baxter-Jones AD, Eisenmann JC, Mirwald RL, Faulkner RA, BaileyDA. The influence of physical activity on lean mass accrual during adolescence: a longitudinal analysis. J Appl Physiol 2008;105:734–41.
12. Weeda J, Horan S, Beck B, Weeks BK. Lifetime physical activity,neuromuscular performance and body composition in healthy young men. Int J Sports Med 2014;35:900–5.
13. Hull HR, Thornton J, Wang J, Pierson RN, Kaleem Z, Pi-Sunyer X,Heymsfield S, Albu J, Fernandez JR, VanItallie TB, et al. Fat-free mass index: changes and race/ethnic differences in adulthood. Int J Obes 2011;35:121–7.
14. Bann D, Kuh D, Wills AK, Adams J, Brage S, Cooper R. Physicalactivity across adulthood in relation to fat and lean body mass in early old age: findings from the Medical Research CouncilNational Survey of HealthandDevelopment,1946–2010.AmJEpidemiol2014;179:1197– 207.
15. Shephard RJ, Park H, Park S, Aoyagi Y. Objectively measuredphysical activity and progressive loss of lean tissue in older Japanese adults: longitudinal data from the Nakanojo study. J Am Geriatr Soc 2013;61:1887–93.
16. Speakman JR, Westerterp KR. Associations between energy demands,physical activity, and body composition in adult humans between 18 and 96 y of age. Am J Clin Nutr 2010;92(4):826–34.
17. Bouchard DR, Beliaeff S, DionneI J, Brochu M. Fat mass but notfat-free mass is related to physical capacity in well-functioning older individuals: nutrition as a determinant of successful aging (NuAge)—the Quebec Longitudinal Study. J Gerontol A Biol Sci Med Sci 2007;62(12):1382–8.
18. Manini TM, Everhart JE, Anton SD, Schoeller DA, Cummings SR,Mackey DC, Delmonico MJ, Bauer DC, Simonsick EM, Colbert LH, et al. Activity energy expenditure and change in body composition in late life. Am J Clin Nutr 2009;90(5):1336–42.
19. Melanson EL, Freedson PS. Physical activity assessment: a review ofmethods. Crit Rev Food Sci Nutr 1996;36:385–96.
20. Speakman JR, Pontzer G, Rood J, Sagayama H, Schoeller DA,Westerterp KR, Wong WW, Yamada Y, Loechl C, Murphy-Alford AJ. The International Atomic Energy Agency international doubly labeled water database: aims, scope and procedures. Ann Nutr Metab 2019;75(2):114–18.
21. Speakman JR, Yamada Y, Sagayama H, Berman ES, Ainslie PN,Andersen LF, Anderson LJ, Arab L, Baddou I, Bedu-Addo K, et al. A standard calculation methodology for human doubly labeled water studies. Cell Rep Med 2021;2:100203.
22. SchoellerDA.Hydrometry.In:RocheAF,HeymsfieldSB,LohmanTG,editors. Human body composition. Champaign, IL: Human Kinetics; 1996. pp 25–43.
23. Forbes GB. Longitudinal changes in adult fat-free mass: influence ofbody weight. Am J Clin Nutr 1999;70(6):1025–31.
24. Forbes GB. The companionship of lean and fat. In: Ellis KJ, EastmanJD, editors. Human body composition. New York: Plenum Press; 1993. p. 3–143.

25. Webster JD, Hesp R, Garrow JS. The composition of excess weight inobese women estimated by body density, total body water and total body potassium. Hum Nutr Clin Nutr 1984;38:299–306.
26. Thomas D, Das SK, Levine JA, Martin CK, Mayer L, McDougallA, Strauss BJ, Heymsfield SB. New fat-free mass - fat mass model for use in physiological energy balance equations. Nutr Metab (Lond) 2010;7:39.
27. Heymsfield SB, Gonzalez MC, Shen W, Redman L, Thomas D. Weightloss composition is one-fourth fat-free mass: a critical review and critique of this widely cited rule. Obes Rev 2014;15:310–21.
28. Quetelet LA. Antropométrie ou mesure des différentes faculties del'homme. Brussels, Belgium: Muquardt; 1871.
29. Cole TJ, Freeman JV, Preece MA. Body mass index reference curvesfor the UK, 1990. Arch Dis Child 1995;73:25–9.
30. Cohn SH, Vartsky D, Yasumura S, Sawitsky A, Zanzi I,Vaswani A, EllisKJ. Compartmental body composition based on total-body nitrogen, potassium, and calcium. Am J Physiol 1980;239:E524–30.
31. Cohn SH, Vaswant A, Yasumura S, Yuen K, Ellis KJ. Assessment ofcellular mass and lean body mass by non-invasive nuclear techniques. J Lab Clin Med 1985;105:305–11.
32. Jackson AS, Janssen I, Sui X, Church TS, Blair SN. Longitudinalchanges in body composition associated with healthy ageing; men, aged 20–96 years. Br J Nutr 2012;107:1085–91.
33. Peterson MD, Sen A, Gordon PM. Influence of resistance exercise onlean body mass in aging adults: a meta-analysis. Med Sci Sports Exerc 2011;43:249–58.
34. Westerterp KR, Meijer EP. Physical activity and parameters of aging: a physiological perspective. J Geront A Biol Sci Med Sci 2001;56: 7–12.
35. Mazzeo RS, Tanaka H. Exercise prescription for the elderly. Sports Med2001;31:809–18.
36. Vitale G, Cesari M, Mari D. Aging of the endocrine system and itspotential impact on sarcopenia. Eur J Int Med 2016;35:10–15.
37. Sipilä S, Narici M, Kjaer M, Pöllänen A, Atkinson RA, HansenM, Kovanen V. Sex hormones and skeletal muscle weakness. Biogerontology 2013;14:231–45.
38. Warden SJ, Mantila Roosa SM, Kersh ME, Hurd AL, Fleisig GS, PandyMG, Fuchs RK. Physical activity when young provides lifelong benefits to cortical bone size and strength in men. Proc Natl Acad Sci U S A 2014;111:5337–42.
39. WardenSJ,MantilaRoosaSM.Physicalactivitycompletedwhenyounghas residual bone benefits at 94 years of age: a within-subject controlled case study. J Musculoskelet Neuronal Interact 2014;14:239–43.
40. Xu L, Nicholson P, Wang Q, Alen M, Cheng S. Bone and muscledevelopment during puberty in girls, a seven-year longitudinal study. J Bone Miner Res 2009;24:1693–8.
41. Weaver CM, Gordon CM, Janz KF, Kalkwarf HJ, Lappe JM, Lewis R, O'Karma M, Wallace TC, Zemel BS. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. Osteoporos Int 2016;27:1281–6.
42. Metcalfe NB, Monaghan P. Compensation for a bad start: grow now,pay later? Trends Ecol Evol 2001;16:254–69.