Physical activity in older adults

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PHYSICAL ACTIVITY IN OLDER ADULTS

Walking economy and circadian pattern

The studies presented in this thesis were performed within NUTRIM School of Nutrition and Translational Research in Metabolism, which is one of the research schools of Maastricht UMC+ (Universitair Medisch Centrum) and participates in the graduate School VLAG (Food Technology, Agrobiotechnology, Nutrition and Health Sciences), accredited by the Royal Netherlands Academy of Arts and Sciences.

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PHYSICAL ACTIVITY IN OLDER ADULTS

Walking economy and circadian pattern

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
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Promotor

Prof. dr. K.R. Westerterp

Copromotor

Dr. A.G. Bonomi (Philips Research, Eindhoven)

Beoordelingscommissie:

Prof. dr. M.K.C. Hesselink, voorzitter

Prof. dr. R.M. Aarts (Philips Research, Eindhoven)

Dr. F.A.J.L. Scheer (Harvard Medical School, Boston)

Prof. dr. L.P.A.J. Schrauwen

Prof. dr. M.S. Westerterp-Plantenga

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Chapter 1

INTRODUCTION

Physical activity is defined as bodily movement produced by skeletal muscles that results in an increase in energy expenditure [1]. Physical activity represents a fundamental vital function that allows mammals to hunt and gather food as well as flee from predators. Human adults are as physically active as mammals of comparable body size [2]. However, the amount of physical activity is largely subject to personal choice and may vary considerably from person to person as well as for a given person over time. After birth, individuals are progressively more active and between age 15 and 20 y physical activity level reaches adult values [3]. After the age of 50 y there is a steady decline of physical activity level [4, 5] (Figure 1.1) and while older adults in their seventh decade spend on average 30 min/day in moderate to vigorous physical activity, individuals older than 80 y are moderately active for only 10 min/day on average [6].

Figure 1.1: Decline in physical activity level (PAL) after the age of 50 years in both men (black circles) and women (grey squares)[5]

Lower physical activity level is associated with reduced mobility and higher mortality risk in older adults [7]. Specifically, a longitudinal study showed that mortality hazard was two to three times higher in older women with low physical activity levels as well as in those with a fast decline in physical activity over a 12-year follow-up [8]. The authors described that obesity, fair or poor health, and mobility disability were among the predictors of a fast decline in physical activity and that walking was one of the activities most likely to decline with increasing age. Given that the western population is rapidly ageing [9], the impact of decreased physical activity on public health poses relevant socio-economic challenges. Preventing chronic and debilitating diseases is the first aim of western

countries health policies for older adults, and the promotion of physical activity is an important component of these policies.

To prevent the decline in physical activity, guidelines suggest that older adults should either be moderately active in bouts longer than 10 minutes for at least 150 min/week [10] or walk at least 10000 steps/day [11]. The benefits of an active lifestyle include the prevention of age-related cardiovascular and metabolic disease [12–14] and the promotion of independent living and well being at older age. However, about half of the western population does not meet the recommendations, due to multiple factors including demographics, health status, cognitive and psychological conditions, behaviour, and environment [15]. To implement effective strategies to increase physical activity, it is important to understand habitual physical activity patterns and determinants of physical activity [16]. The description of patterns and types of physical activity requires objective monitoring of physical activity in daily life.

Measures of physical activity

Methods for the assessment of physical activity have evolved from behavioural observation and self-report (questionnaires and activity diaries) to physiological markers (heart rate, body temperature, ventilation), motion sensors (pedometers, accelerometers), and indirect calorimetry [17]. The laws of physics dictate that energy is required to perform (mechanical) work and therefore physical activity should lead to a measurable increase in energy expenditure [18].

The doubly labelled water technique (DLW) is a calorimetric method that provides measures of total energy expenditure (TEE) in free-living conditions over a time interval of at least one week [19]. Two measures of physical activity can be derived by combining TEE with resting energy expenditure (REE): physical activity level and activity energy expenditure. Physical activity level (PAL) is the expression of TEE as a multiple of REE

$$PAL = \frac{TEE}{REE}$$

while activity energy expenditure (AEE) can be calculated as

$$AEE = (0.9 * TEE) - REE$$

This calculation assumes diet-induced thermogenesis to be 10% of TEE [20–22].

From the DLW technique, accurate measure of PAL and AEE can be derived [23, 24], but no information on physical activity patterns is available in terms of frequency, duration, and intensity [17]. The DLW technique has become the reference for the validation and comparison of methods to monitor physical activity

patterns [17, 25]. Accelerometry is the most promising method to objectively assess physical activity patterns [17, 21]. Accelerometers are small, lightweight and therefore unobtrusive devices able to quantify physical activity by measuring the acceleration of the human body during movement [26]. Relative to self-report methods, accelerometers provide more accurate assessments of physiological or mechanical parameters that correspond to physical activity [27]. However, many accelerometers perform poorly compared to DLW [20] and so far only three of the validated accelerometers, Actigraph GT3X, Dynaport, and TracmorD have been able explain more than 50% of the variation of PAL or AEE [17]. A DLW validated accelerometer has been indicated as the alternative for doubly labelled water, to assess the PAL of a subject in daily life [21]. Among the advantages of accelerometers is the detail in which the pattern, and intensity of activity can be monitored over days, weeks, or longer [27].

Walking

Walking is the most common physical activity among physically active adults [28], although its contribution to PAL has not been quantified yet. Maintenance of independent walking can be integral to quality of life [29] for it allows accomplishing the tasks of daily living [30] and it facilitates social interactions [29]. Walking speed has been proposed as a vital sign [31] for its potential to predict future health status [32, 33] and functional decline [34] and life expectancy [35]. Slow preferred walking speed is associated with declining functional capacity [36], reduced balance confidence [37] and increased fall risk [38]. Ageing is accompanied by a decline in preferred walking speed [39], and in walking activity contributing to the age-related decline in physical activity [8] and the increase in fall risk [40].

An aspect that characterises walking is its economy or cost, i.e. the steady-state energy expenditure for a given sub-maximal speed of walking [41]. Walking cost is quantified as the energy above resting required to displace 1 kg of body mass over 1 meter [42]. The relationship between walking cost and speed is different for each individual and it can be described as a u-shaped function with a minimum between 0.9 and 1.4 m/s [43–46] (Figure 1.2). The speed with minimum walking cost has been defined as optimal walking speed and it approximates subjects' preferred walking speed [47, 48]. Ageing is associated with an increase in walking cost [44, 48, 49], walking instability [50, 51] and impaired biomechanics [52].

Walking cost is minimised through biomechanical strategies aimed at reducing muscle activation [53]. For example, the interaction of the limbs with the ground is organised in order to shorten the duration of muscle forces needed to move forward. Additionally, potential energy is stored in the tissues of the stance limb and it is subsequently released during propulsion to reduce the active production of mechanical energy by the muscles [54]. The combination of this type of

Figure 1.2: Relationship between walking cost (Cost of Transport) and walking speed measured in young (●) and older adults (▽) [49]

strategies, together with the coordination of acceleration and deceleration of body segments [55], produces a smooth velocity profile of body segments with reduced and more regular acceleration of the centre of body mass [42].

Accelerometers have been used to measure cycle by cycle variations in gait rate and regularity of gait cycles [56], showing that decreased regularity of acceleration patterns is associated with ageing and fall risk [57]. Walking cost might therefore be determined by body accelerations as measured with an accelerometer, providing new insights useful to develop intervention strategies to delay the age related increase in walking cost and the decline in physical activity.

Physical activity recognition

Physical activity recognition has emerged in the last decade as a topic of interest in several fields such as activity monitoring, population screening, and home care for older adults [58]. Wearable technologies, such as an accelerometer can provide a considerable amount of information, allowing the development of recognition algorithms [59]. A number of different features of the raw acceleration signal have been considered for activity recognition. Heuristic features are those derived from the understanding of the relationship between one activity and its acceleration output. For example, walking is a cyclic behaviour and therefore produces a cyclic output in contrast with noncyclic behaviours such as posture transitions [60]. The

cyclic acceleration of each body segment during walking has a predictable shape in healthy individuals [61–63] (Figure 1.3). Thus, the acceleration template is a feature that might contribute to recognition models. Nevertheless, one’s body acceleration during walking might to a certain extent deviate from the template [64]. Because of these inter-individual variations, personalised templates are a more promising feature than standard templates. Physical activity recognition based on personalised heuristic features of activities might allow the detection of walking in daily life in order to describe walking as a component of physical activity in older adults.

Figure 1.3: Typical acceleration patterns of different body segments of a healthy individual during walking [61]

Circadian patterns

Several biological processes show endogenous and adjustable patterns of about 24h, known as circadian patterns [65]. The regulation of these patterns is controlled by the suprachiasmatic nucleus (SCN), which is located in the hypothalamus and behaves as an oscillator. This behaviour of the SCN is responsible for the synchronisation of several “suboscillators”, each of which regulates one or more circadian processes [66, 67].

A typical example of a suboscillator is the pineal gland [68–70], which releases

melatonin during the hours of darkness, thus following a circadian pattern [71, 72]. Melatonin is a hormone that signals the biological night and regulates the circadian pattern of sleep and wakefulness [73]. Wake time comprises most of the physical activity and therefore also physical activity shows a circadian pattern with skeletal muscles having a ‘molecular clock’ as their suboscillator [74]. Young healthy adults show marked and regular circadian patterns with high peaks of melatonin at night [75], about 8 hours of consolidated sleep [76] and sustained activity during wake time [77]. With increasing age, melatonin levels decrease [78], sleep decreases and becomes more disrupted [79, 80] and physical activity level declines [5]. Furthermore, the patterns of activity during wake time show significant changes with age [16].

Patterns of activity can be studied by means of accelerometers, giving insight into how activity levels vary over the course of the day. A typical pattern of activity shows a peak of activity in the morning between 10:00 and 11:00 followed by a decrease during the rest of the day [81]. Older adults show decreased physical activity and increased sedentary behaviour especially in the morning and have a diminished ability to maintain relatively high intensity physical activity [16]. Further insights into activity patterns through the day could help in defining strategies for increasing physical activity level.

Interventions

Strategies for intervention aimed at improving health outcomes and reducing all-cause mortality at older age include: nutrition, physical activity, physiotherapy, and psychological support [82]. Of the proposed aspects, physical activity interventions such as regular exercise [83, 84] are among the most promising [82] and studied [85, 86]. Exercise is defined as physical activity that is planned, structured and repetitive [1]. Exercise is a preventive public health intervention [87] for its effects on several outcomes such as reducing all-cause mortality [85], cardiovascular disease [88], fall risk [89], and cognitive impairment [90]. Fitness training exercise as conducted in a fitness centre [91] is generally divided in three categories. Resistance or strength training aims at increasing strength and muscle mass [92]. This type of training in older adults can therefore counteract sarcopenia [93], which naturally occurs with ageing [94], and can improve stability [95]. Stretching exercises improve flexibility, joint range of motion and proprioception with consequent effects on balance and stability [96, 97]. Finally, endurance training aims at improving cardiovascular conditioning and results in increased maximal oxygen uptake [98], reduced recovery time [99] and increased metabolic efficiency during exercise [100]. Combinations of fitness training types, known as multicomponent fitness training, have been shown to be most efficient to address a broad range of outcomes in healthy older people [101–104]. However, further research is needed to determine the effect of multicomponent fitness training on

specific aspects of physical activity such as walking cost.

Outline of the thesis

This thesis aims at *providing further insights into physical activity in older adults with a focus on walking and circadian pattern and on the effect of multicomponent fitness training on walking cost*. The first study describes the calibration of an accelerometer designed to estimate physical activity level in daily life (**Chapter 2**). An accelerometer worn in daily life can provide information about specific activities, such as walking, and their contribution to physical activity level. Based on recordings of raw body accelerations in daily life, the importance of walking as a component of physical activity in older adults was described (**Chapter 3**). Accelerometer output combined with indirect calorimetry measures were analysed to detect determinants of walking economy from body acceleration during walking in an ageing population (**Chapter 4**). Subsequently, the effect of one-year multicomponent fitness training on walking cost was investigated (**Chapter 5**). **Chapter 6** compares circadian patterns of physical activity in older adults with a wide range of PAL, in order to help designing new strategies to increase physical activity. Finally, **Chapter 7** examined the relation between quality of sleep and overnight energy expenditure.

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Chapter 2

**VALIDATING MEASURES OF
FREE—LIVING PHYSICAL ACTIVITY IN
OVERWEIGHT AND OBESE SUBJECTS
USING AN ACCELEROMETER**

VALENTI G, CAMPS SG, VERHOEF SP, BONOMI AG, WESTERTERP KR

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Abstract

Background Free-living physical activity can be assessed with an accelerometer to estimate energy expenditure but its validity in overweight and obese subjects remains unknown.

Objective Here, we validated published prediction equations derived in a lean population with the Tracmor_D accelerometer (DirectLife, Philips Consumer Lifestyle) in a population of overweight and obese. We also explored possible improvements of new equations specifically developed in overweight and obese subjects.

Design Subjects were 11 men and 25 women (age: 41 ± 7 years; BMI: 31.0 ± 2.5 kg/m²). Physical activity was monitored under free-living conditions with Tracmor_D, whereas total energy expenditure was measured simultaneously with doubly-labeled water. Physical activity level (PAL) and activity energy expenditure (AEE) were calculated from total energy expenditure and sleeping metabolic rate.

Results The published prediction equation explained 47% of the variance of the measured PAL ($p < 0.001$). PAL estimates were unbiased (errors (bias $\pm$ 95% confidence interval): 0.02 ± 0.28). Measured and predicted AEE/body mass were highly correlated ($r^2 = 58\%$, $p < 0.001$); however, the prediction model showed a significant bias of 8 kJ/kg per day or 17.4% of the average AEE/ body mass. The new prediction equation of AEE/body mass developed in the obese group showed no bias.

Conclusions Equations derived with the Tracmor_D allow valid assessment of PAL and AEE/body mass in overweight and obese subjects. There is evidence that estimates of AEE/body mass could be affected by gender. Equations specifically developed in overweight and obese can improve the accuracy of predictions of AEE/body mass.

Introduction

Physical inactivity results in reduced activity energy expenditure (AEE), which contributes to positive energy balance. A prolonged positive energy balance leads to weight gain and therefore to overweight and obesity. Guidelines suggest that weight loss and maintenance should combine dietary therapy with an AEE of at least 5–8 MJ per week [1]. These guidelines report that the promotion of physical activity and increased AEE is an important aspect of intervention strategies for weight maintenance after weight loss. Accurate assessments of AEE are therefore necessary to describe and promote long-term interventions. Techniques for estimating AEE should imply minimal discomfort for the subjects and must be validated under free-living conditions.

The gold standard for measurements of free-living total energy expenditure (TEE) is the doubly labelled water technique (DLW) [2]. Physical activity level (PAL) and AEE can be derived from TEE combined with basal metabolic rate, that is, the energy requirement of vital functions. When PAL and AEE are derived from DLW, no insight into physical activity patterns can be provided. Furthermore, studies based on DLW usually include relatively small populations. Accelerometers, instead, can provide physical activity patterns in large populations when they can accurately estimate AEE and PAL under free-living conditions [3].

Over 20 prediction equations developed with accelerometers have been validated to assess energy expenditure under free-living conditions [4]. These validation studies are conducted mostly in healthy lean adults. The results reported cannot be extended to overweight populations before their generalisability is verified with a specific validation. Only two of the equations validated in lean subjects have been tested in overweight and obese. In 1998, Fogelholm et al. estimated DLW measurements of TEE from the Caltrac accelerometer with unpublished built-in algorithms in 20 overweight women [5]. They reported a weak correlation ($r^2=0.11$, $p=0.15$) between measured and predicted TEE owing to the fact that an accelerometer cannot assess basal metabolic rate, which constitutes about 60% of TEE [6]. We consider that an estimation of AEE from accelerometer data would have been more appropriate. Furthermore, the Caltrac was worn only on days 1, 3, 6, 8 and 12 of the DLW measurement period of 14 days. This systematic selection of the measurement days could have affected the results. More recently, Jacobi et al. validated the TR3 accelerometer in 13 overweight subjects to estimate AEE simultaneously with DLW measurements [7]. The study reported a significant correlation ($r^2=0.45$, $p<0.05$) between measurements and estimates of AEE. However, AEE was not adjusted for individual differences in body size, which could explain why it was concluded that the TR3 could provide accurate estimations only at a group level. Furthermore, the small group size

and the limited variance of AEE (2.9 ± 0.9 MJ per day) could have reduced the predictive value of the accelerometer. Other accelerometers like the DynaPort (DynaPort MiniMod; McRoberts B.V., The Hague, The Netherlands) were used in studies involving obese subjects without validation in overweight and obese under free-living conditions against DLW [8].

The aim of this study was to validate published prediction equations derived in a lean population [9] with the Tracmor_D accelerometer (DirectLife, Philips Consumer Lifestyle, Amsterdam, The Netherlands) to estimate free-living AEE and PAL in overweight and obese subjects with DLW as the reference. We also explored possible improvements of new equations specifically developed in overweight and obese subjects.

Subjects and methods

Subjects Subjects were 11 men and 25 women, aged 41 ± 7 years and body mass index (BMI) 31.0 ± 2.5 kg/m² (Table 2.1). All subjects were included in the final analysis. Written informed consent was obtained and the Ethics Committee of the Maastricht University Medical Center approved the study. The study was registered in ClinicalTrials.gov (registration number: NCT01015508).

Table 2.1: Subject characteristics (values are mean $\pm$ SD)

Gender (m/f)	11/25
Age (years)	41 ± 7
Height (m)	1.71 ± 0.09
Body mass (kg)	90.3 ± 10.7
BMI (kg/m²)	31.0 ± 2.4
Tracmor_D (MCounts per day)	1.54 ± 0.41
Wearing days (days)	11 ± 3
Wearing time (h per days)	16 ± 1
TEE (MJ per days)	12.3 ± 2.0
SMR (MJ per days)	6.9 ± 0.9
AEE (MJ per days)	4.1 ± 1.2
AEE_{kg} (kJ/kg per day)	46 ± 13
PAL	1.77 ± 0.19

Abbreviations: AEE, activity-related energy expenditure; AEE_{kg}, AEE divided by body mass; BMI, body mass index; PAL, physical activity level (TEE/SMR); SMR, sleeping metabolic rate; TEE, total energy expenditure; Tracmor_D, Tracmor_D output.

Study design The study included a two-week measurement period of physical activity with Tracmor_D. TEE was measured simultaneously with DLW. At the beginning of the study, subjects spent one night in a respiration chamber. The morning after, and before breakfast, anthropometric measurements were taken. Body mass was measured on an electronic scale (Life Measurement Corporation Inc., Concord, CA, USA) to the nearest 0.01 kg. Height was measured to the nearest 0.1 cm.

Energy expenditure Sleeping metabolic rate (SMR) was measured during an overnight stay in a respiration chamber. The chamber is an airtight room that measures 14 m³ and is furnished with bed, table, chair, freeze toilet, washing bowl, radio, television and a computer [10]. Subjects entered the chamber at 21:00 and left the chamber at 07:30 the following morning. Subjects were not allowed to eat during their stay in the chamber. Energy expenditure was calculated from O₂ consumption and CO₂ production according to Brouwer's formula [11]. SMR was defined as the lowest observed energy expenditure for three consecutive hours during the night. Room temperature was held constant at 20±1 °C.

TEE was measured using DLW according to the Maastricht protocol [12]. Briefly, after the collection of a baseline urine sample on the evening of day 0, subjects drank a weighted amount of ²H₂¹⁸O. The result is an initial increase in the body water enrichment of about 120 p.p.m. for ²H and about 240 p.p.m. for ¹⁸O. Urine samples were then collected in the mornings (from the second voiding) of days 1, 8 and 15, and in the evening of days 1, 7 and 14. PAL and activity-related energy expenditure (AEE) were then derived from TEE measured with DLW. PAL was calculated as

$$PAL = \frac{TEE}{SMR}$$

AEE was calculated as

$$AEE = (0.9 * TEE) - SMR$$

assuming the diet-induced thermogenesis to be 10% of TEE [13] and was then adjusted for body mass (BM):

$$AEE_{kg} = \frac{AEE}{BM}$$

Accelerometry Free-living activity was monitored from days 1 to 14 with Tracmor_D (DirectLife, Philips Consumer Lifestyle) positioned on the lower back using a belt, as described before [9]. Subjects reported in a diary periods in which the Tracmor_D was not worn. At the end of the measurement, data were downloaded from the Tracmor_D using dedicated software (DirectLife, Philips

Consumer Lifestyle). The output was expressed in activity counts per minute. Counts per day were calculated integrating counts per minute over each day. Average counts per day were calculated over the days of measurement. Days during which data were missing or subjects carried the accelerometer for less than 10 h were excluded and the average was calculated on the remaining data, considering daily physical activity an ergodic process. Subjects with at least two valid days were included. Following these criteria, no subject was excluded.

Data analysis Two simple linear equations developed by Bonomi et al., based on average daily counts, were applied to our population to cross-validate the estimations of PAL and AEE_{kg} (activity-related energy expenditure divided by body mass) [9]. The criteria were the measurements of PAL and AEE_{kg} based on indirect calorimetry methods, as described before. In addition, we explored possible improvements of developing specific equations in our population. The new equations were calculated with two simple linear regressions, with counts as independent variable and the criteria as dependent variables. All overweight and obese subjects were included in the training of the equations. Estimation errors of all equations were calculated as difference between estimations and criteria. Standard error of the estimate (SEE) was calculated as the root mean square of the errors. Pearson's sample correlation coefficient was used to test agreement between estimations and measurements, as well as between errors and BMI. Squared correlation coefficient between dependent and independent variables was calculated as coefficient of determination (simple linear regression). All variables were expressed as mean $\pm$ standard deviation (SD). The level for statistical significance was set at $p<0.05$.

Results

Subjects were overweight and obese adults with a predominance of female subjects (Table 2.1). The Tracmor_D was worn 13 ± 1 days during 15 ± 2 h per day indicating a high compliance. On average 12 ± 3 days were valid. Gender or other subject characteristics did not influence the compliance.

Validation of published equations The prediction equation of PAL significantly explained the variance of the measured values ($r=0.69$, $p<0.001$). The estimates were unbiased with an average error of -0.02 ± 0.14 that corresponded to $-1.1\pm8.0\%$ of the average PAL. This resulted in an SEE of 0.14 or 8.0% of the average PAL (Table 2.2). Errors were correlated with measured PAL ($r=-0.84$, $p<0.001$) but not with BMI ($r=0.01$, $p>0.5$).

Measured and predicted AEE_{kg} were highly correlated ($r=0.76$, $p<0.001$); however, the prediction model showed a significant bias of 8 ± 8 kJ/kg per day

Table 2.2: Explained variation and errors statistics of the prediction equations previously validated in lean subjects [9] applied to a population of overweight and obese ($N = 36$), in comparison with the newly developed equation

Parameter	AEE _{kg} (kJ/kg per day)		PAL	
	Published equation	New equation	Published equation	New equation
r	0.76*	0.76*	0.69*	.69*
SEE				
Value	11	8	0.14	0.14
Rel (%)	24.9	17.4	8.0	8.0
ME				
Value	8	—	-0.02	—
Rel (%)	17.4	—	-1.1	—
Linear trend	-0.57*	-0.65*	-0.84*	-0.73*

Abbreviations: AEE_{kg}, activity-related energy expenditure divided by body mass; ME, mean error; PAL, physical activity level (total energy expenditure/ sleeping metabolic rate); r, correlation between estimated and measured values; Rel, relative value as a percentage of the mean measure; SEE, standard error of the estimate; Linear trend, linear correlation between errors and reference values as a measure of systematic linear bias. * $p < 0.001$.

or $17.4 \pm 17.4\%$ of the average AEE_{kg} ($p < 0.0001$). This resulted in an SEE of 11 kJ/kg per day (24.9% of the average AEE_{kg}). Estimation errors correlated with measures ($r = -0.57$, $p < 0.001$) but not with BMI ($r = 0.01$, $p > 0.5$).

Development of new prediction equation The explained variance of the new prediction equation of PAL ($r = 0.69$, $p < 0.001$) was the same as the earlier equation applied to overweight and obese subjects. The variance and the SEE did not reduce with respect to the published equations (SEE = 0.14 or 8.0% of the average PAL). Errors were correlated with measured PAL ($r = -0.73$, $p < 0.001$) but not with BMI ($r = 0.01$, $p > 0.05$) (Figure 2.1).

As in the published prediction equation applied to overweight and obese subjects, measured AEE_{kg} and predictions from the new equation were highly correlated ($r = 0.76$, $p < 0.001$). In the new equation, the variance of the error did not reduce with respect to the published equation (8 kJ/kg per day or 17.4% of the average AEE_{kg}), reducing the SEE to 8 kJ/kg per day. Estimation errors correlated with AEE_{kg} measures ($r = -0.65$, $p < 0.001$) but not with BMI ($r = 0.01$, $p > 0.5$).

Figure 2.1: **Regressions, equations and residual plots (mean error and confidence interval) of the prediction equations of activity-related energy expenditure divided by body mass (AEE_{kg}) and PAL developed in overweight and obese subjects**

Discussion

The aim of this study was to validate published Tracmor_D equations to estimate free-living AEE in overweight and obese subjects with DLW as the reference. We also explored possible improvements of new equations specifically developed in overweight and obese subjects. Forty-seven percent of the variance of PAL and 58% of the variance of AEE_{kg} were explained by the prediction equations, which were the highest explained variances reported so far in free-living overweight and obese subjects. Equations specifically developed for overweight and obese subjects did not lead to significant improvements in the estimates and errors.

The explained variation of PAL was statistically significant and comparable between the population of overweight and obese subjects and the population of lean subjects (47%, $p < 0.001$ vs. 46% $p < 0.001$). The estimates of PAL in our population were unbiased and the variance of the error was comparable to the one reported by Bonomi et al. [9] in lean subjects, which resulted in a similar SEE (0.14 vs. 0.13). Furthermore, the PAL prediction equation specifically developed for overweight and obese subjects did not lead to a relevant improvement in the

estimates errors. Thus, our study extends the validity of the published equation to estimate PAL from the Tracmor_D to a population of overweight and obese.

In 2011, Assah et al. reported that an Actiheart could explain only from accelerations 29% ($p=0.001$) of the variance of AEE_{kg} in African adults with an SEE of 38 kJ/kg per day and a significant bias of 27 kJ/kg per day [14]. The authors concluded that the Actiheart could estimate AEE_{kg} . In the current study, estimates of AEE_{kg} explained a higher percentage of the variance of AEE_{kg} (58%, $p<0.001$) with a lower SEE (11 kJ/kg per day) and a lower bias (8 kJ/kg per day). When compared with the study of Bonomi et al. [9], the explained variance found in our population was slightly higher (58% vs. 50%). This resulted in a lower variance of the error, which compensated for the bias, and resulted in an SEE lower than the one reported by Bonomi (11 vs. 12 kJ/kg per day). Another consequence of an increased explained variance was that the new estimation equation for AEE_{kg} from activity counts had a reduced variance of the errors. Because the variance of the errors was lower, SEE was also reduced (11 vs. 8 kJ/kg per day). This reduction, although significant, was practically irrelevant as we consider 11 kJ/kg per day a reasonable SEE and the reduction to 8 kJ/kg per day would require further studies to be extended to other populations. Thus, the development of a specific equation is not necessary to improve the estimations in our population. The validity of the AEE_{kg} prediction equation derived with Tracmor_D in lean subjects is therefore extended to overweight and obese.

The bias found for the AEE_{kg} estimates was proportionally larger than the one for PAL estimates (17% vs. 1%). This fact can be explained by comparing SMR and subject characteristics between the overweight and obese population and the lean used to develop the prediction equations (Table 2.1). An increased SMR would be expected from subjects with a higher body mass and therefore a higher fat free mass. Nevertheless, the gender distribution in the two populations was not equal: there was a predominance of male subjects in the lean population and a predominance of female subjects in the overweight and obese group. Female subjects are known to have a lower percentage of fat free mass, which compensated in the overweight and obese population for the increase in weight [15]. The result of this was an overcorrection of AEE in overweight and obese subjects, leading to artificially low measured values and therefore a positive bias and an increased SEE. This result did not affect the calculation of PAL as it is derived only from TEE and SMR and it does not require adjustment for body size. There is therefore evidence that estimates of AEE_{kg} could be affected by gender when comparing subjects with a wide range of BMI. For this reason, in the quantification of physical activity, PAL should be preferred to AEE_{kg} or gender should be included in a more complex model.

A negative linear trend was found between errors of AEE_{kg} and PAL when compared with the measured values. This means that subjects with a low level of physical activity were overestimated and vice versa, resulting in a bigger variance

of the error. However, the SEE of AEE_{kg} and PAL were consistent with those reported in lean subjects and we can assume that this linear trend would not restrict the applicability of the method in free-living subjects.

A limitation of this study is the assumption that activity counts and energy expenditure are linearly related. This assumption is generally accepted and it implies the possibility to estimate AEE_{kg} or PAL from daily activity counts using a linear equation. Nevertheless, it has been shown that an a priori classification of the type of activity can improve the assessments of energy expenditure [16]. Simpler classification models have been developed to deal with the nonlinearity between accelerometer output and energy expenditure. Crouter et al. classified the activities into two categories [17, 18]. They developed from this classification a two-regression model that was shown to be more accurate than a simple linear model for estimating METs. However, this more computationally sophisticated technique has not yet been shown to be valid in obese subjects as it was validated under free-living conditions in a population of mostly non-obese subjects (BMI 25.0 ± 4.6 , range 19.3–37.4 kg/m²). Applying a similar method to the Tracmor_D might improve the estimation error described in this study both in lean and in overweight and obese populations.

In conclusion, our study showed that two published equations derived with Tracmor_D allow valid assessment of physical activity in overweight and obese subjects with low errors. In particular, the explained variance of the dependent variables was the highest reported so far in free-living overweight and obese subjects. Validity of PAL and AEE_{kg} prediction equations developed in lean subjects is therefore extended to subjects with high BMI. There is evidence that estimates of AEE_{kg} could be affected by gender when comparing subjects with a wide range of BMI. Tracmor_D can be reliably used to monitor increasing levels of physical activity in overweight and obese subjects.

Conflict of interests

AGB is employed at Philips Research Laboratories. The remaining authors declare no conflict of interest.

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Author contributions

KRW and SPMV designed the study. SGJAC and SPMV collected the data. GV analysed the data and wrote the manuscript. KRW and AGB contributed to the interpretation of the data and reviewed the manuscript. The study was executed under supervision of KRW. All authors read and approved the final manuscript.

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Chapter 3

WALKING AS A CONTRIBUTOR TO PHYSICAL ACTIVITY IN HEALTHY OLDER ADULTS

VALENTI G, BONOMI AG, WESTERTERP KR

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Abstract

Background Physical activity is recommended to promote healthy ageing. Defining the importance of activities such as walking in achieving higher levels of physical activity might provide indications for interventions.

Objective To describe the importance of walking in achieving higher levels of physical activity in older adults.

Methods The study included 42 healthy subjects aged between 51 and 84y (BMI 25.6 ± 2.6 kg/m²). Physical activity, walking and non-walking activity were monitored with an accelerometer during 2 weeks. Physical activity was quantified by accelerometer-derived activity counts. An algorithm based on template matching and signal power was developed to classify activity counts into non-walking counts, short walks counts and long walks counts. Additionally, in a subgroup of 31 subjects energy expenditure was measured using doubly labeled water to derive physical activity level (PAL).

Results Subjects had an average PAL of 1.84 ± 0.19 (range 1.43–2.36). About 20% of the activity time ($21 \pm 8\%$) was spent walking, which accounted for about 40% of the total counts ($43 \pm 11\%$). short bouts composed $83 \pm 9\%$ of walking time, providing $81 \pm 11\%$ of walking counts. A stepwise regression model to predict PAL included non-walking counts and short walk counts, explaining 58% of the variance of PAL (SEE=0.12). Walking activities produced more counts per minute than non-walking activities ($p < 0.001$). Long walks produced more counts per minute than short walks ($p = 0.001$). Non-walking counts were independent from walking counts ($r = -0.05$, $p = 0.38$).

Conclusions Walking activities are a major contributor to physical activity in older adults. Walking activities occur at higher intensities than non-walking activities, which might prevent individuals from engaging more walking activity. Finally, subjects who engage more walking activities do not tend to compensate by limiting non-walking activities.

Introduction

Ageing is accompanied by reduced physical activity (PA) and increased sedentary behaviour [1–3]. The time spent by older adults in moderate to vigorous PA declines from 30 minutes/day in individuals in their seventh decade, down to 10 minutes/day in individuals older than 80 years [4]. Reduced PA is associated with reduced mobility [5] and decreased life expectancy [6, 7]. To contrast this trend, the World Health Organisation guideline suggests that subjects older than 65 years should be moderately active for at least 150 minutes/week in bouts longer than 10 minutes [8]. Although a variety of activities are carried out during the day, it is unknown which one is more effective in increasing PA.

Among the activities of daily living, walking is of major importance. Walking is an indicator of overall well-being and walking speed is an indicator of life expectancy. Independent living strongly depends on walking, which allows individuals to accomplish many tasks of daily living [9]. Furthermore, walking is a highly prevalent form of PA in healthy older individuals, who reportedly walk as much as when they were younger and more physically active [10]. In spite of its relevance, the role of walking in PA has not yet been described and it is unclear whether active people actually walk more. Individuals who frequently engage walking activities might compensate by decreasing non-walking activities, such as biking, practicing sports, house-holding or climbing stairs, ultimately resulting in similar levels of PA as individuals less inclined to walk. The definition of the role of walking in PA might provide more activity-specific insights as well as intervention indications.

Quantification of walking activity can be provided by inertial sensors such as pedometers [11, 12] or accelerometers [13, 14]. Both pedometers and accelerometers offer the possibility to monitor walking activities over time. Pedometers only measure number of steps, whereas more information including non-walking activities, might be derived from accelerometers. To date, studies where walking patterns are described by means of an accelerometer have not integrated the results of overall PA, leaving out the effects of non-walking activities [15, 16].

This study aimed at describing the importance of walking in achieving higher levels of PA, as measured using doubly labeled water in older adults.

Methods

Population The population included 35 subjects from a previous study and 7 subjects with similar characteristics [17]. All 42 healthy subjects (19 males and 23 females) aged between 51 and 84y (body mass index (BMI) 25.6 ± 2.6 kg/m²) were recruited by advertisements in local newspapers (Table 3.1). After signing a written informed consent form, respondents completed a questionnaire

including information regarding orthopaedic conditions, neurological disorders and cardiovascular problems that could affect the study. The questionnaire was discussed during a medical visit with a doctor. All subjects were in good orthopaedic, neurological and cardiovascular health and were therefore included. The study was conducted according to the Declaration of Helsinki and the Ethics Committee of the Maastricht University Medical Center approved the study. This trial was registered at ClinicalTrials.gov as NCT01609764.

Table 3.1: Subject characteristics (N=42, 19 males)

	Mean±SD	Range
Age (years)	65±8	51–84
Height (m)	1.69±0.10	1.47–1.89
Body mass (kg)	73±11	40–95
BMI (kg/m²)	25.6±2.6	18.6–30.0

Abbreviations: BMI, body mass index; SD, standard deviation.

Study design Physical activity, walking and non-walking activity were monitored with an accelerometer for 2 weeks. Additionally, total energy expenditure and basal metabolic rate were measured in a representative subgroup of 31 randomly selected subjects. Physical activity level (PAL) was then calculated as ratio between total energy expenditure and basal metabolic rate [18].

Walking recognition algorithm Subjects wore a tri-axial accelerometer (GT3X+, ActiGraph, Pensacola, FL) on the lower back using a belt, as described before [18]. Accelerometry data were collected in the laboratory and in daily life at a sampling rate of 60 Hz. During the laboratory session, subjects performed treadmill walking at 4 different speeds. Such data were used to define parameters of the algorithm used to detect walking activities. A personalised template prototype of the acceleration signal was derived from the treadmill data for each subject as described before [17]. Accelerometer data were analysed as vector magnitude and segmented into epochs of 5 seconds. The acceleration signal from each epoch was cross-correlated with the personalised template. The standard deviation of the acceleration signal (SD_s) and the standard deviation of the cross-correlation function output (SD_{cc}) were calculated for all epochs. SD_s and SD_{cc} from treadmill epochs were used to fit two probability distributions indicating the likelihood of walking. A Naïve Bayes probability distribution for the laboratory walking data was defined as follows:

$$P(\text{walk}) = P(\text{walk}|SD_s \wedge SD_{cc})$$

$$P(\text{non-Walk}) = 1 - P(\text{walk})$$

Assuming naïve conditional independence,

$$P(\text{walk}) = k * P(\text{SD}_s|\text{walk}) * P(\text{SD}_{cc}|\text{walk})$$

with

$$k = \frac{P(\text{walk})}{P(\text{SD}_s \wedge \text{SD}_{cc})}$$

$P(\text{SD}_s|\text{walk})$ and $P(\text{SD}_{cc}|\text{walk})$ were derived from the data and k was empirically estimated as

$$k = \frac{0.5}{0.14 * \max(P(\text{SD}_s \wedge \text{SD}_{cc}|\text{walk}))}$$

The classifier for each epoch in daily life was constructed as follows:

$$Y = \text{argmax}(P(\text{walk}), P(\text{non-walk}))$$

Bouts of walking shorter than one minute were classified as short walks, whereas bouts lasting at least one minute were classified as long walks. Counts were calculated by integrating body accelerations of each epoch after detrending and rectification of the signal from each axis. Epochs with less than 10^{-3} counts/seconds were labeled as inactivity and excluded from further analysis.

Non-walking counts, short walk counts, and long walk counts per day were calculated integrating counts in the respective epochs over each day. Walking counts were the sum of short walk counts and long walk counts. Activity counts were the sum of walking counts and non-walking counts. Time spent in each category was measured as 5 seconds times the respective number of epochs. Days during which data were missing or subjects carried the accelerometer for less than 10 hours were excluded and the average was calculated for the remaining data, assuming that daily PA is an ergodic process where the expected mean does not change after removing a randomly taken sample. Average counts per day were calculated over the days of measurement.

Energy expenditure Total energy expenditure (TEE) was measured during the 2 weeks of measurement using doubly labeled water, according to the Maas-tricht protocol [19]. Briefly, after the collection of a baseline urine sample on the evening of day 0, subjects drank a weighted amount of $^2\text{H}_2^{18}\text{O}$. The result is an initial increase in the body water enrichment of about 120 ppm for ^2H and about 240 ppm for ^{18}O . Urine samples were then collected in the morning (from the second voiding) of days 1, 8 and 15, and in the evening of days 1, 7 and 14. Samples were analysed by isotope ratio mass spectrometry (Optima; VG Isogas, Middlewich, Cheshire, UK). Carbon dioxide production was calculated from the difference between the elimination rates of ^2H and ^{18}O . Total daily energy

expenditure was calculated from carbon dioxide production [20], assuming a respiratory quotient of 0.85. Basal metabolic rate (BMR) was measured during 30 minutes under a ventilated hood (Omnical, Maastricht Instruments, Maastricht, The Netherlands) on the morning of the first day of measurement in the supine position under standard conditions of rest, fasting, immobility, thermoneutrality and mental relaxation.

Data analysis All variables are expressed as mean $\pm$ SD. The normality of the data was examined with the Shapiro–Wilk test. The Pearson correlation coefficient (r) was used to describe the association between variables. A linear regression was used to model the relation between activity counts and PAL. The residuals of the model were studied to identify confounding factors. The best predictors of PAL among non–walking counts, short walk counts and long walk counts were selected using a stepwise multi–linear regression. The statistical significance threshold was set at $p < 0.05$. MATLAB (MathWorks Inc, Natick, MA, USA) was used for the data elaboration and the figures. SPSS (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

Results

PAL ranged between 1.43 and 2.36 (1.84 ± 0.19 on average, $N=31$). The activity time of the total group ($N=42$) was on average 10.5 ± 1.7 hours/day. About 20% of the activity time ($21 \pm 8\%$) was spent in walking activities, which accounted for about 40% of the total counts ($43 \pm 11\%$) (Figure 3.1). The average walking time was about 2 hours/day, indicating that PA was not restricted in this population. Subjects walked in short bouts for $83 \pm 9\%$ of their walking time providing $81 \pm 11\%$ of their walking counts (Table 3.2).

Table 3.2: Physical activity and walking activity ($N=42$). Mean $\pm$ SD

	Time (min/d)	Counts (kCnts/d)	Intensity (Cnts/min)
Physical activity	630 ± 101	6.2 ± 1.4	9.8 ± 1.2
Non–walking activity	500 ± 97	3.5 ± 1.1	7.0 ± 1.2
Walking activity	130 ± 61	2.7 ± 0.9	21.5 ± 3.0
Walks <1 min	106 ± 49	2.1 ± 0.7	20.9 ± 3.1
Walks >1 min	24 ± 17	0.6 ± 0.4	23.3 ± 3.6

Abbreviations: SD, standard deviation.

Figure 3.1: **Composition of activity time and activity counts in older adults (N=42)**

Higher PAL was achieved by subjects with higher activity time ($r=0.75$, $p<0.001$) and activity counts ($r=0.73$, $p<0.001$). Specifically, subjects with a higher PAL spent more time in non-walking activities ($r=0.64$, $p<0.001$) and produced more non-walking counts ($r=0.61$, $p<0.001$) than subjects with a lower PAL. The correlation coefficient between PAL and walking, particularly during short walks, was positive but did not reach significance (PAL vs. walking time: $r=0.26$, $p=0.08$; PAL vs. walking counts: $r=0.33$, $p=0.07$; PAL vs. short walk counts: $r=0.35$, $p=0.05$).

Two linear models were developed to identify the best predictors of PAL. A simple linear model based on activity counts could explain 52% of the measured PAL ($SEE=0.13$). The residuals of this model correlated with the fraction of walking time spent in short walks ($r=-0.38$, $p=0.02$), suggesting that the prevalence of short walks might be a determinant of PAL. Therefore, a stepwise regression model was developed to predict PAL from one or more variables among non-walking counts, short walk counts and long walk counts (Table 3.3). This second model included non-walking counts and short walk counts, explaining 58% of the variance of PAL ($SEE=0.12$).

Walking activities were conducted at higher intensities than non-walking activities (21.5 ± 3.0 counts/minutes vs. 7.0 ± 1.2 counts/minutes, $p<0.001$). Among walking activities, long walks were conducted at higher intensities than short walks (23.3 ± 3.6 counts/minutes vs. 20.9 ± 3.1 counts/minutes, $p=0.001$). Walking counts were independent from non-walking counts ($r=-0.05$, $p=0.38$), (Figure 3.2).

Table 3.3: Two prediction equations of physical activity level from accelerometer counts

Variable	Coefficient	p-val	r ²	SD	Beta
Linear model					
Intercept	1.24	<.001		0.11	
Physical Activity Model	9.70x10 ⁻⁵	<.001	0.53	1.71x10 ⁻⁵	0.73
			0.53		
Multiple linear model					
Intercept	1.17	<.001		0.11	
Non-walking Activity	10.92 x10 ⁻⁵	<.001	0.38	1.99 x10 ⁻⁵	0.68
Walks <1 min	13.42 x10 ⁻⁵	.001	0.20	3.64 x10 ⁻⁵	0.46
Model			0.58		

Abbreviations: Variable, variables included in the model; p-val, significance level; r², coefficient of determination; SD, standard deviation of the coefficient, Beta, standardised coefficient.

Discussion

This is the first study that combines accelerometry and the doubly labeled water method to show that walking activities are a major contributor to PA in a population of older adults with a wide range of PAL.

The range of PAL of the subjects in this study is higher than normally reported in healthy older adults [21–23]. The activity time, including all levels of PA, was 10.5 hours/day, which is lower than previous studies where sedentary, moderate and vigorous activities were reported to add up to 14 hours/day [24], when measured with an accelerometer in older adults. Although different, the results are compatible as in previous studies sedentary time also included periods of inactivity. This instead excluded inactivity time to focus on PA and in particular on walking.

Walking was a main component of PA providing more than 40% of the activity counts. Despite the relevant proportion of counts, walking time was about 20% of activity time or 2 hours/day. Previous studies reported similar lengths of time spent walking in healthy and independently living older adults [25]. The relevance of walking in daily life is well established [26, 27], and walking activity measured with pedometers is often used as a proxy of PA [28, 29]. To our knowledge no study has assessed walking activity as counts so far, preferring number of steps. The number of steps is not comparable to activity counts, whereas the assessment of walking activity as walking counts described in this study allowed to describe the contribution of walking to activity counts. The results showed that walking counts are a relevant proportion of activity counts, although walking time was a

Figure 3.2: **Walking counts vs. non-walking counts in older subjects (N=42)**

relatively small portion of activity time. The short amount of time spent walking is possibly the reason why walking counts only showed a trend with PAL but did not reach significance. Although walking does not seem to explain variations in PAL, its contribution in terms of counts produced remains a major one.

The discrepancy between the proportion of walking counts and the proportion of walking time implies that walking activities occurred at higher intensities and produced more counts per unit of time, compared with non-walking activities. Walking counts have not been reported before, but previous studies reported that during walking older adults reach 80% of their maximum heart rate and oxygen consumption, concluding that walking intensity in this population is moderate to high [30]. Similarly, it can be observed that long walks were performed at higher intensities than short walks, but over a shorter portion of time. It seems therefore that older adults prefer low intensity activities and that the high intensity discourages them from engaging in walking and, in particular, long walks. This conclusion is supported by previous studies where walking time in daily life was shown to decrease with increasing intensity [25].

Subjects who engaged in more walking activities did not compensate by reducing non-walking activities. Although previous studies suggest that PA interventions could suffer from compensatory behaviours outside the exercise time [31–33], these results show that walking is independent of non-walking. It is therefore reasonable to hypothesise that walking could be less prone to

compensatory behaviours and therefore a good candidate for PA interventions.

There is ongoing discussion about whether PA interventions should focus on long walks or short walks [34–36]. The results of this study suggest that subjects tend to prefer shorter walks because of their relatively lower intensity. Short walks also contribute to explaining the variation in free-living PAL and therefore subjects who engaged in more short walks showed higher PAL. These might suggest that short walk interventions could be better tolerated by older individuals and effectively increase their PAL.

The ability of accelerometers to differentiate between activities allowed the detection of walking in this study. Other activities, such as biking, swimming, rowing, deskwork, housekeeping, or driving, have different acceleration patterns and were classified as non-walking activities. Algorithms to detect these activities have been described before [37–40] and they could be used to divide the non-walking category into more specific categories. Given that non-walking counts partly explained the inter-individual variance in PAL, the detection of different non-walking activities can provide a more elaborate insight into the composition and determinants of PA.

The population in this study was representative for an active and healthy older population. The findings cannot be generalised to populations with different characteristics without specific studies. Similar protocols could be used in populations that might benefit from increased PA such as obese individuals, diabetic patients, or white-collar workers. Interventions focused on walking in these populations might be effective, but more research is needed to quantify possible compensatory behaviours and to investigate other factors that can contribute to physical activity level, such as environmental factors, socioeconomic status, and health status.

This study provides reference values for the contribution of walking to PA in healthy older adults, as measured with wearable devices. One possible application to e-health is in the promotion of PA. A wearable device can reveal subjects' proportion of walking in daily life and provide them with motivational feedbacks.

The results of a previous study suggested that subjects with different walking economy produce different acceleration outputs [17]. This might have implications on the relationship between PAL and activity counts. Future studies might reveal whether walking economy can improve the prediction of PAL with an accelerometer.

In conclusion, walking activities are a major contributor to PA in older subjects with a wide range of PAL, but the relatively high intensity of walking might prevent individuals from engaging in more walking activity. It is also shown that subjects who engage in more walking activities do not tend to compensate by limiting non-walking activities.

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Authors' Contributions

KRW and GV designed the study. GV collected the data, analysed the data and wrote the manuscript. KRW and AGB contributed to the interpretation of the data and reviewed the manuscript. The study was executed under the supervision of KRW.

Everyone who contributed significantly to the work has been listed. All authors read and approved the final manuscript.

Conflict of interests

None declared.

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Chapter 4

BODY ACCELERATION AS INDICATOR FOR WALKING ECONOMY IN AN AGEING POPULATION

VALENTI G, BONOMI AG, WESTERTERP KR

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Abstract

Background In adults, walking economy declines with increasing age and negatively influences walking speed. This study aims at detecting determinants of walking economy from body acceleration during walking in an ageing population.

Methods 35 healthy elderly (18 males, age 51 to 83 years, BMI 25.5 ± 2.4 kg/m²) walked on a treadmill. Energy expenditure was measured with indirect calorimetry while body acceleration was sampled at 60 Hz with a tri-axial accelerometer (GT3X+, ActiGraph), positioned on the lower back. Walking economy was measured as lowest energy needed to displace one kilogram of body mass for one meter while walking (WCost_{min}, J/kg/m). Gait features were extracted from the acceleration signal and included in a model to predict WCost_{min}.

Results On average WCost_{min} was 2.43 ± 0.42 J/kg/m and correlated significantly with gait rate ($r^2=0.21$, $p<0.01$) and regularity along the frontal (antero-posterior) and lateral (mediolateral) axes ($r^2=0.16$, $p<0.05$ and $r^2=0.12$, $p<0.05$ respectively). Together, the three variables explained 46% of the inter-subject variance ($p<0.001$) with a standard error of estimate of 0.30 J/kg/m. WCost_{min} and regularity along the frontal and lateral axes were related to age (WCost_{min}: $r^2=0.44$, $p<0.001$; regularity: $r^2=0.16$, $p<0.05$ and $r^2=0.12$, $p<0.05$ respectively frontal and lateral).

Conclusions The age associated decline in walking economy is induced by the adoption of an increased gait rate and by increasingly irregular body acceleration in the horizontal plane.

Introduction

Walking is a periodic motor task that allows a body to move over a distance [1]. Characteristics of walking such as walking speed, gait rate and regularity change with age: elderly show reduced walking speed and regularity together with increased gait rate [2]. These changes result from declining fitness and decreased walking stability and are associated with fall risk [3, 4]. Results of decreased walking speed and increased fall risk include functional decline with a reduction of life expectancy of up to 30% between similar aged subjects with different walking speeds [5–11].

Together with reduced walking speed, ageing is associated with low walking economy, i.e. increased walking cost [12]. Walking cost is quantified as the energy required to displace 1 kg of body mass over 1 meter and follows a u-shaped relation with walking speed, showing a minimum between 0.9 m/s and 1.4 m/s [13–16]. The walking speed at which the minimum is measured has been defined as optimal walking speed and approximates subjects' preferred walking speed [17, 18]. A gradual increase of minimum walking costs begins after the 50th year of age and progressively speeds up after the age of 65 years possibly leading to reduced mobility in elderly [15, 19, 20]. It has been suggested that increased walking cost together with diminished energetic capacity could contribute to the decline of walking speed [19, 21].

The walking cost is minimised by reducing muscle activation through precise sequencing of muscle activation and coordination of acceleration and deceleration of body segments [22]. The result of this strategy is a smoother velocity profile of body segments with reduced and more regular acceleration of the centre of body mass [23, 24]. Ageing affects the coordination and the strength of muscles and therefore body accelerations and walking economy might be related in elderly. In particular, the age-related reduction in walking economy could be reflected in irregular acceleration of the centre of body mass, and result in reduced walking speed.

Wearable sensors such as accelerometers are able to collect continuous data and have been used to measure cycle by cycle variations in gait rate and regularity of gait cycles [25], showing that decreased regularity of acceleration patterns is associated with ageing and fall risk, functional decline and eventually mortality [26–30]. The trunk and limbs play a critical role in the regulation body acceleration during walking [31]. Symmetrical walks can be modeled as an inverted pendulum where the body mass is concentrated in a virtual point called centre of mass. This model describes the cinematic strategy to preserve mechanical energy by periodically transforming kinetic energy into potential energy and vice versa. The lower back is the closest position to the centre of body mass. Asymmetrical walks deviate from this model and changes in limbs movements have to compensate for

the deviations and maintain stability. This results in increased energy expenditure and decreased walking economy in asymmetrical walks. Nevertheless, healthy subjects show symmetrical walking patterns and therefore their walking patterns can be described by the inverted pendulum model and by the accelerations of the centre of body mass. Although an interaction between trunk acceleration and walking economy has been hypothesised, simultaneous measurements of energy expenditure and body acceleration during walking have not been reported yet [32, 33].

The current study aims at detecting determinants of walking economy from body acceleration during walking in an ageing population in order to define innovative indicators for functional performance and fall risk.

Subjects and methods

Subjects Thirty-five healthy subjects (18 men and 17 women) aged 51 to 83, 64 ± 8 years on average were recruited by advertisements in local newspapers (Table 4.1). After signing a written informed consent, respondents completed a questionnaire including orthopaedic conditions, neurological disorders and cardiovascular problems that could affect the study. The questionnaire was discussed during a medical visit with a doctor. All subjects were in good orthopaedic, neurological and cardiovascular conditions and were therefore included. The study was conducted according to the Declaration of Helsinki and the Ethics Committee of the Maastricht University Medical Centre approved the study. This trial was registered at www.clinicaltrials.gov as NCT01609764.

Study design The testing protocol included standing and walking on a treadmill at selected speeds encompassing the preferred speed. Four walking speeds at regular intervals were chosen out of six: 0.28 m/s, 0.56 m/s, 0.83 m/s, 1.11 m/s, 1.39 m/s and 1.67 m/s. The protocol started at 0.83 m/s and was increased every 5 minutes by 0.28 m/s. If the subject was able to walk all 4 speeds up to 1.67 m/s without running, the test ended. Instead, if the walking speed exceeded subject's running threshold, the test was continued at the lower speeds to obtain 4 speeds at regular intervals for each subject. Subjects wore a mask to measure energy expenditure and an accelerometer on the lower back to measure regularity of acceleration patterns of gait and step rate. Tests were performed in the morning, when subjects were fasted and had not undergone intense physical activity.

Energy expenditure During the protocol, oxygen consumption and carbon dioxide production were measured with an indirect calorimeter (Omnical, Maastricht Instruments, Maastricht, The Netherlands). Calculation of total energy

Table 4.1: Subject characteristics (Mean $\pm$ SD)

Gender (m/f)	18/17
Age (years)	64 $\pm$ 8
Height (m)	1.70 $\pm$ 0.10
Body mass (kg)	73.8 $\pm$ 11.7
BMI (kg/m²)	25.5 $\pm$ 2.4
Walking economy (J/kg/m)	2.43 $\pm$ 0.42
Step Length (m)	0.65 $\pm$ 0.9
Gait Rate (Hz)	0.91 $\pm$ 0.09
Regularity (%)	
	Vertical 29 $\pm$ 7
	Lateral 51 $\pm$ 13
	Frontal 43 $\pm$ 12

Abbreviations: BMI, body mass index; Walking economy, the lowest energy needed to displace one kilogram of body mass for one meter while walking; Regularity, deviations of body accelerations from a personalised template as a percentage of the variance of the template. Lower values indicate higher regularity.

expenditure from O_2 consumption and CO_2 production was based on Brouwer's formula [34].

For each subject, total energy expenditure was averaged over the plateau during the last 2 minutes of standing and of each walking speed. The energy expenditure of standing was subtracted from total energy expenditure to calculate walking energy expenditure. Walking cost was defined as the energy needed to displace one kilogram of body mass for one meter while walking, and it was calculated as walking energy expenditure normalised for walking speed and for body mass. The minimum walking cost ($WCost_{min}$) was considered for further analysis and the speed at which it was measured was defined as optimal walking speed.

Body acceleration During the protocol, body accelerations were sampled at 60 Hz, with a GT3X+ (ActiGraph, Pensacola, FL) positioned on the lower back using a belt. Tri-axial body acceleration data were downloaded and exported to Matlab (Mathworks, Natick, MA). The reference axes of the data (x, y, z) were aligned to the anatomical axes (vertical, lateral, frontal). Only the data recorded during the last two minutes of the optimal walking speed was considered for further analysis. Gait rate was calculated as the peak in the power spectrum density of the vertical axis, calculated between 0.5 and 1.5 Hz.

Regularity of acceleration patterns of gait Regularity of acceleration patterns of gait was quantified as deviation of the acceleration from a personalised template. For each subject, acceleration peaks in the vertical direction were identified at approximately twice the gait rate and used to detect foot contact with the ground. Acceleration of each gate cycle included samples between two consecutive contacts of the same foot. Gait cycles were re-sampled to the slowest gait cycle allowing a uniform number of samples and avoiding aliasing. After aligning all gait cycles, means and standard deviations of corresponding samples were calculated. The sequence of the means formed a personalised template of the acceleration patterns of gait (Figure 4.1). The standard deviation of the means was a measure of the power of the template, while the average of the standard deviations was a measure of deviation of all gait cycles from the template [35]. Regularity was calculated as the ratio between the deviation of all gait cycles from the template and the power of the template, expressed as a percentage. Lower percentage indicates higher regularity and vice versa.

Statistical analysis Stepwise multiple-linear regression analysis was used to include the best independent variables including gait rate and regularity in the three directions to predict $WCost_{min}$. Squared Pearson product-moment correlation coefficient (r^2) was used to describe associations between variables. Data elaboration was conducted in MATLAB®. Regression analysis was conducted in SPSS®. All variables are expressed as mean±standard deviation (SD). The significance threshold was set to $p<0.05$.

Results

The optimal walking speed, i.e. the walking speed with the lowest walking cost, was on average 1.18 ± 0.16 m/s. No significant difference between male and female (18 males vs 17 females) was found in age, optimal speed or $WCost_{min}$, therefore they were analysed together.

On average $WCost_{min}$ was 2.43 ± 0.42 J/kg/m and correlated significantly with gait rate ($r^2=0.21$, $p<0.01$) and regularity along the frontal and lateral axes ($r^2=0.16$, $p<0.05$ and $r^2=0.12$, $p<0.05$ respectively). Together, the three variables explained 46% of the inter-subject variance ($p<0.001$, Figure 4.2) with a standard error of estimate of 0.30 J/kg/m, which was 13% of the average $WCost_{min}$. The model is described in Table 4.2; variables are presented in order of inclusion.

A significant correlation was found between $WCost_{min}$ and age ($r^2=0.44$, $p<0.001$), and between estimated $WCost_{min}$ and age ($r^2=0.32$, $p<0.01$). Decreasing regularity along the frontal and lateral axes was positively related with age ($r^2=0.16$, $p<0.05$ and $r^2=0.12$, $p<0.05$ respectively).

Table 4.2: Stepwise regression of the minimum walking cost, with an accelerometer in elderly. Variables are presented in order of inclusion.

Variable	Coefficient	Significance	r^2	SEE (J/kg/m)
Intercept	-0.699	–		
Gait Rate	2.300	$p < 0.005$		
Regularity Lateral	1.254	$p < 0.01$		
Regularity Frontal	0.941	$p < 0.05$		
Model			0.46	0.30

Abbreviations: Variable, variables included in the stepwise regression; r^2 , squared correlation between estimates and measures; SEE, standard estimation error; Regularity Lateral, deviations of body accelerations from a personalised template in the lateral direction. Lower values indicate higher regularity; Regularity Frontal, deviations of body accelerations from a personalised template in the frontal direction. Lower values indicate higher regularity.

Discussion

The study showed that the age related decline in walking economy is associated with the adoption of an increased gait rate and by irregular body acceleration in the horizontal plane. Estimates of $WCost_{min}$ from step rate and regularity in the horizontal plane could describe part of the covariance between walking economy and age.

Measures of $WCost_{min}$ and gait rate (2.43 ± 0.42 J/kg/m and 0.91 ± 0.09 J/kg/m respectively; mean $\pm$ SD) were in line with the literature [36, 37]. Decreased walking economy, measured as increased $WCost_{min}$, was positively related with gait rate ($r^2 = 0.21$, $p < 0.01$). A higher gait rate implies that more steps are made per unit of distance explaining the increase of $WCost_{min}$. Higher gait rate is associated to shorter step length which characterises a less destabilising gait [38]. It is therefore concluded that a decreased walking economy is associated with a destabilising gait.

A significant relation was found between $WCost_{min}$ and regularity along the frontal and lateral axes ($r^2 = 0.16$, $p < 0.05$ and $r^2 = 0.12$, $p < 0.05$ respectively) while regularity in the vertical direction didn't influence $WCost_{min}$. Decreased regularity in the horizontal plane may result from reduced control of the movements, which may lead to instability in the horizontal plane. Possible causes are increased stiffness of the articulations and loss in muscle mass which have been reported in elderly [36]. The reduced regularity in the horizontal plane could have induced elderly to increase gait rate with a consequent rise in $WCost_{min}$.

A step-wise multilinear model, including step rate and regularity in the horizontal plane, could estimate $WCost_{min}$ and could describe part of the covari-

Figure 4.1: **Example of two acceleration templates in the lateral direction with twice the standard deviation of all steps from the template.** The first example refers to a younger subject (55 years old) while the second refers to an older one (83 years old). Regularity was quantified as the Standard Deviation From the Template, Expressed as a Percentage of the Standard Deviation of the Template. Lower values indicate higher regularity. SD, standard deviation of all steps from the template; Template, average of all steps.

ance between walking economy and age ($WCost_{min}$ and age: $r^2=0.44$, $p<0.001$; $WCost_{min}$ estimates and age $r^2=0.32$, $p<0.01$). Step rate and regularity in the horizontal plane could therefore partly determine the age-related increase in $WCost_{min}$. The unexplained part of covariance instead could be due to the age related increase in co-activation of antagonist muscles, which would rise the cost of walking [36] without necessarily affecting the acceleration patterns of gait. Furthermore, co-activation of antagonist muscles has been shown to be a compensatory response to unstable conditions [39] and can therefore be a consequence of the reduced regularity in the horizontal plane.

A limitation of this study is that muscle activity during walking was not measured. Measures of muscle activity could have described how ageing induces less stable and therefore less efficient walking in this population. Nevertheless the measurement of muscle activity requires electrodes placed on the lower limbs, which would alter one's gait cycle and consequently affect the cost of walking.

Figure 4.2: **Predicted minimum walking cost as a function of measured values with the line of identity.** r^2 , squared correlation between estimates and measures.

All the tests were conducted inside a laboratory to increase the accuracy of the results. The generalisation of these results to daily life requires further studies in order to provide further insight in the ageing process, and to prevent and delay functional decline and increased fall risk associated with ageing.

Increased fall risk is one of the most common co-morbidities related to ageing [40–42]. Reduced walking speed is an indicator of fall risk [5–9] and is related to reduced walking economy [19, 21]. Interest in fall risk assessment in daily life with unobtrusive accelerometers is increasing. Laboratory measures of acceleration during standing or during walking have been proposed to discriminate between fallers and non-fallers, although validation in daily life is required [43]. The results of this study suggest that changes in walking economy can be detected with an accelerometer. Given that walking economy is related to walking speed and therefore fall risk, these results might suggest that regularity in the horizontal plane could contribute to fall risk assessment. In this population fall risk was not evaluated, but further studies focusing on the capability of the described determinants to detect increased fall risk could allow the design of specific interventions to prevent subjects' falls.

Future studies could aim at extending these results in daily life where they might contribute to the prediction of falling risk. The features described in this study could be measured in older adults with a history of falls and older

adults with no history of falls. This would reveal a possible direct relation between the features and fall risk. In case this relation was confirmed, the features could be implemented in devices capable of detecting falls in free living [44–46]. Simultaneous measure of the features and of fall history would allow a quantification of the predictive power of the features for fall risk. Future studies could also define the mechanisms behind the effect of irregular body acceleration on walking economy by including measures of muscle activations. Possibly, wireless systems could reduce the obtrusiveness of most current electromiographic systems.

In conclusion, increased gait rate and by irregular body acceleration in the horizontal plane contribute to the age associated decline in walking economy. A waist-worn accelerometer can assess regularity of body acceleration and estimate walking economy, with possible applications in fall prevention and the delay of functional decline in the elderly.

Author contributions

Conceived and designed the experiments: KRW GV. Performed the experiments: GV. Analysed the data: GV. Contributed reagents/materials/analysis tools: GV KRW. Wrote the paper: GV KRW AGB.

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Chapter 5

MULTICOMPONENT FITNESS TRAINING IMPROVES WALKING ECONOMY IN OLDER ADULTS

VALENTI G, BONOMI AG, WESTERTERP KR

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Abstract

Background Walking economy declines with increasing age, possibly leading to mobility limitation in older adults. Multicomponent fitness training could delay the decline in walking economy.

Purpose This study aimed to determine the effect of multicomponent fitness training on walking economy in older adults.

Methods Participants were untrained adults, age 50 to 83 yr (N=26, 10 males, age = 63 ± 6 yr, BMI = 25.6 ± 2.1 kg/m²). A control group was also recruited (N=16, 9 males, age = 66 ± 10 yr, BMI = 25.4 ± 3.0 kg/m²), matching the intervention group for age, weight, body composition, and fitness. The intervention group followed a multicomponent fitness program of 1 h, twice per week during 1 yr. The control group did not take part in any physical training. Fat-free mass, walking economy, and maximal oxygen uptake ($\dot{V}O_{2\max}$) were measured in both groups before and after the year. Walking economy was measured with indirect calorimetry as the lowest energy needed to displace 1 kg of body mass for 1 m while walking on a treadmill. The data were compared between the two groups with repeated-measures ANOVA.

Results Thirty-two subjects completed all measurements. There was an interaction between the effects of time and group on $\dot{V}O_{2\max}$ ($p < 0.05$) and walking economy ($p < 0.05$), whereas fat-free mass did not change significantly ($P = 0.06$). $\dot{V}O_{2\max}$ decreased by 1.8 ml/kg/min in the control group and increased by 1.3 ml/kg/min in the intervention group. The lowest energy needed to walk increased by 0.12 ml/kg/min in the control group and decreased in the intervention group by 0.13 ml/kg/min.

Conclusions Multicomponent fitness training decreases walking cost in older adults, preserving walking economy. Thus, training programs could delay mobility limitation with increasing age.

Introduction

Ageing is associated with reduced physical activity [1, 2] and loss of independent functioning [3]. Low physical activity in older adults is due to multiple factors such as increased fatigue, reduced energy reserve [4, 5], decreased maximal aerobic capacity [6], and increased energetic cost of daily life activities [7]. Increased cost of daily life activities results in lower energy reserve [8, 9], which possibly undermines independent functioning. Delaying the increase in cost of daily life activities would induce higher energy reserve, likely prolonging independent functioning in older adults.

Walking represents the most frequent daily life activity and it allows individuals to carry out simple and fundamental tasks [10]. Measures of walking ability such as walking speed have been designated as functional vital sign [11]. Higher walking speed at older age indicates preserved functional and health status and it is related to lower death rates [12]. Older adults with low walking speed tend to show higher walking cost, requiring more energy to displace 1 kg of body mass for 1 meter while walking [13].

Walking cost, assessed as total energy expenditure during walking minus standing energy expenditure divided by distance and body mass [8], follows a U-shaped relation with walking speed with a minimum between 0.9 m/s and 1.4 m/s [8]. The walking speed at which the minimum is measured approximates subjects' preferred walking speed and is therefore the condition that best represents daily life conditions [14, 15]. The minimum walking cost increases gradually after the 50th year of age, possibly leading to reduced mobility in older adults [16–18].

Several factors have been suggested to contribute to the age-related decline in walking economy, such as strength, sarcopenia, loss of neuromuscular coordination, and decreased regularity of walking patterns. Sarcopenia leads to a decline in muscle strength and power. Augmenting muscle power to contrast the decline in muscle strength during walking can decrease walking cost and increase preferred walking speed [19]. At the same time, the age-related decline in neuromuscular coordination can alter the pattern of recruitment of muscles and the timing of limb movements, inducing compensatory strategies requiring increased energy [20]. Furthermore, irregular body acceleration in the horizontal plane is associated with increased walking cost [21]. Interventions that address these aforementioned factors could indirectly reduce the cost of walking. Fitness training might be an effective strategy to reach these effects.

Fitness training is generally divided in three categories, all of which could indirectly improve walking economy. Resistance training can counteract sarcopenia [22], which naturally occurs with ageing [23], by increasing muscle mass, strength [24] and stability [25] and thus decrease walking cost [26]. Stretching exercises improve flexibility, joint range of motion and proprioception with consequent

effects on balance and stability [27, 28] which might result in reduced walking cost. Endurance training aims at improving cardiovascular conditioning and results in increased maximal oxygen uptake as well as reduced recovery time [29, 30]. After an endurance training program, individuals showed decreased heart-rate [31] and energy expenditure during exercise [32]. Multicomponent fitness training is a combination of resistance stretching and endurance training [33, 34] and it might incorporate the benefits of these training categories, resulting in improved walking economy.

Given the importance of delaying the age-related decline in walking economy to maintain independence and quality of life and to mitigate health risks in older adults, this study aimed at determining the effect of one-year multicomponent fitness training on walking economy in older adults.

Methods

Subjects Untrained adults, aged 50 to 83 years ($N=26$, 10 males, age 63 ± 6 y, body mass index (BMI) 25.6 ± 2.1 kg/m²) were recruited for the fitness training through advertisements in local newspapers. A control group ($N=16$, 9 males, age 66 ± 10 y, BMI 25.4 ± 3.0 kg/m²) was recruited similarly matching for age, weight, body composition and fitness level. Subjects of both groups signed a written informed consent and subsequently completed and discussed with a medical doctor a questionnaire covering orthopaedic conditions, neurological disorders and cardiovascular problems that could affect the study. All subjects were in good orthopaedic, neurological and cardiovascular conditions. The study was conducted according to the Declaration of Helsinki and the Ethics Committee of the Maastricht University Medical Center approved the study. This trial was registered at www.clinicaltrials.gov as NCT01609764.

Study design Body mass, fat-free mass (FFM), walking economy and maximal oxygen uptake ($\dot{V}O_{2\max}$) normalised for body mass were measured at baseline and after one year. During this year, the intervention group followed a fitness program, while the control group was not enrolled in any fitness training and maintained the habitual physical routine.

Body composition Body mass was measured with subjects in underwear after an overnight fast on an electronic scale (Life Measurement Corporation Inc., Concord, CA, USA) to the nearest 0.01 kg.

FFM was derived from body mass and total body water using the deuterium dilution method as described in the Maastricht protocol [35].

Walking economy Walking economy was measured as lowest energy needed to displace one kilogram of body mass for one meter while walking on a treadmill. Subjects walked on a treadmill at four speeds while wearing a mask to measure energy expenditure, following a previously described protocol [21]. Briefly, subjects started with five minutes standing followed by walking at 0.83 m/s. Walking speed was increased every five minutes by 0.28 m/s. If the subject was able to walk at four speeds up to 1.67 m/s without running, the test ended; otherwise the test was continued at 0.56 m/s to obtain four speeds at regular intervals for each subject. O_2 consumption and CO_2 production were measured with an indirect calorimeter (Omnicol, Maastricht Instruments, Maastricht, The Netherlands). The calorimeter has an automatic (30 min cycle) calibration system using certified span gas (1% certificate) and zero gas (N_2 at 99.999% purity). The accuracy of the output data was verified weekly with a methanol-burning test as previously recommended for similar systems [36]. Calculation of total energy expenditure from O_2 consumption and CO_2 production was based on Brouwer's formula [37]. Total energy expenditure was averaged over the plateau during the last 2 minutes of standing and of each walking speed. Walking cost was defined as the energy needed to displace one kilogram of body mass for one meter while walking, and it was calculated as total energy expenditure minus standing energy expenditure, normalised for walking distance and for body mass. The minimum walking cost ($WCost_{min}$, J/kg/m) was considered for further analysis.

Maximal oxygen uptake Maximal oxygen uptake was measured following an incremental protocol [38]. To guarantee the independence of the measure from walking economy, the test was performed on a cycle ergometer. Furthermore, the use of a cycle ergometer is safer for older subjects, compared to a treadmill [39, 40]. A warming up workload of 75 W for men and 50 W for women was maintained for 5 minutes and then increased by 50 W every 2.5 min. The increase in workload was reduced to 25 W when the respiratory quotient was higher than one or when heart-rate reached a value of 35 bpm below the age-predicted maximal heart-rate (220 bpm-age). The test continued until exhaustion. A mask covering mouth and nose was used to collect expired air which was continuously analysed for O_2 consumption and CO_2 production (Omnicol, Maastricht Instruments, Maastricht, The Netherlands).

Intervention The intervention group followed a group fitness program of one hour, at least two times per week during one year, available at a local fitness centre. Classes of the program were held in the morning from Monday until Thursday. Subjects were asked to participate on two non-consecutive days every week. Subjects were allowed to miss at most 10% of the lessons along the year, allowing a cumulative five weeks of holidays or sickness over the one-year study.

The fitness instructor who coached every class designed the program specifically for participants over 50 years of age. Each class started with a warming up of 15 minutes during which participants performed moderate intensity free-body aerobic exercises accompanied by music. Subsequently, subjects exercised for 30 minutes in a resistance circuit training of moderate intensity using weight stack machines. Three sets of 15 repetitions were performed of the following exercises: chest press, lateral row, pull down, triceps extension, biceps curl, leg press, leg curl, abdominal crunch. Each class ended with 15 minutes of cooling down including core, stretching and balance exercises of low intensity, accompanied by music. The instructor supervised all subjects, assessing their participation and promoting a progressive increase of the training load. A researcher visited periodically the fitness centre during hours of class to motivate subjects and to collect feedback from the instructor about participation and training progress. Subjects participating in less than two sessions per week were contacted and motivated to resume regular participation in the program.

Data analysis The data were compared between the two groups with two-way repeated measures ANOVA with two factors (time and group) and two levels per factor (Month 0–Month 12, Intervention–Control). The number of levels assured that the assumption on the sphericity of the data was verified. Post-hoc analysis was not considered because the number of levels of both factors was only two. All variables were expressed as mean $\pm$ standard deviation (SD). The statistical significance threshold was set at $p<0.05$.

Results

Six (three males) out of 16 control subjects dropped out during the study and were excluded from the analysis. Four (one male) out of 26 intervention subjects were excluded from the study due to insufficient adherence to the intervention. Thirty-two subjects completed all measurements. Males and females did not differ in age, optimal speed or $WCost_{min}$, and were analysed together. Subject characteristics at baseline did not differ between groups (Table 5.1).

Four subjects could not walk at 1.67 m/s and walked at 0.56 m/s to obtain four speeds at regular intervals for each subject. The optimal walking speed, i.e. the walking speed with the lowest walking cost, at baseline was 1.18 ± 0.16 m/s and was not significantly different between groups. The relationship between walking cost and speed at baseline is presented in Figure 5.1.

There was a statistically significant interaction between the effects of time and group on $\dot{V}O_{2max}$ ($p<0.05$) and walking economy ($p<0.05$). $\dot{V}O_{2max}$ increased in the intervention group by 1.3 ml/kg/min and decreased in the control group by 1.8 ml/kg/min (Table 5.1). The cost of walking increased in the control group

Table 5.1: Subject characteristics at baseline and after 12 months of the control group and the intervention group (Mean $\pm$ SD)

Gender (m/f)	Control		Intervention	
	6/4		9/13	
	Month 0	Month 12	Month 0	Month 12
BM (kg)	72.1 $\pm$ 14.8	73.6 $\pm$ 17.1	73.9 $\pm$ 10.8	74.1 $\pm$ 10.4
FFM (kg)	51.2 $\pm$ 12.2	51.3 $\pm$ 12.5	50.5 $\pm$ 9	52.3 $\pm$ 9.8*
BMI (kg/m ²)	24.8 $\pm$ 3.2	25.2 $\pm$ 3.9	25.6 $\pm$ 2.1	25.7 $\pm$ 2.2
$\dot{V}O_{2\max}$ (l/min)	2.19 $\pm$ 0.78	2.07 $\pm$ 0.63	2.04 $\pm$ 0.50	2.15 $\pm$ 0.52†
$\dot{V}O_{2\max}$ /BM (ml/kg/min)	30.1 $\pm$ 8.7	28.2 $\pm$ 7.5	27.6 $\pm$ 4.9	28.9 $\pm$ 4.9†
Absolute WCost _{min} (J/m)	174 $\pm$ 37	186 $\pm$ 58	176 $\pm$ 31	167 $\pm$ 26†
WCost _{min} (J/kg/m)	2.47 $\pm$ 0.58	2.59 $\pm$ 0.85	2.39 $\pm$ 0.35	2.26 $\pm$ 0.28†

Abbreviations: BM, body mass; FFM, fat-free mass; BMI, body mass index; WCost_{min}, the lowest energy needed to displace one kilogram of body mass for one meter while walking; *, significant time effect ($p < 0.05$); †, significant group:time effect ($p < 0.05$).

along the year by 0.12 J/kg/m, which was about 5% of the initial cost of walking. Subjects who followed the fitness training showed the opposite tendency, with a reduction of the cost of walking of 0.13 J/kg/m which was more than 5% of the initial cost of walking and resulted in a 13% lower waking cost than the control group (Figure 5.2). Total body mass was maintained stable during the study. Fat-free mass had the tendency to increase in the intervention group although the time-group interaction did not reach significance ($p = 0.06$).

Discussion

The results of the study showed that, after one-year of multicomponent fitness training, the energetic cost of walking in older adults decreased significantly compared to a control group. The training increased $\dot{V}O_{2\max}$, improving the aerobic capacity of trained older adults compared to the decline shown by a control group. Less energy needed for walking might promote sustained physical activity and contribute to prolong the independence of trained older adults from external aid for daily life activity.

Approximately 85% of the subjects recruited for the intervention complied with the intervention while 63% of the control subjects completed the study. Previous studies including one-year fitness training interventions reported compliances of about 50% [41, 42]. One explanation for the higher compliance in the current study might be the average good health of the subjects, with an average $\dot{V}O_{2\max}$ of 27.6 $\pm$ 4.9 ml/kg/min at baseline and a BMI of 25.7 $\pm$ 2.5 kg/m² [43]. Healthy

Figure 5.1: **Relationship between walking cost and speed, at baseline.** Subjects walked at regular speed intervals between 0.56 m/s and 1.39 m/s (slow walkers, $N=4$) or between 0.83 m/s and 1.67 m/s (quick walkers, $N=28$). Solid lines represent means and dotted lines represent standard deviations.

individuals are likely to perceive the benefits of an active lifestyle and this might have contributed to the high compliance to the training. Other possible explanations for the higher compliance are the initial motivation of subjects and the social aspect of a group fitness program. Most of the intervention subjects were motivated by the opportunity to engage in some physical activity. Many of them referred that being part of a study gave them an external motivation and helped them maintaining their fitness routine. Participation was possibly also promoted by the fact that the training was financed by the university and had no economical effect on the subjects. At the end of the study, most of the intervention subjects expressed the intention to continue independently the fitness training at the fitness centre. The factors that influenced this decision were the stimulating environment provided by a group lesson and the purpose of preserving the physiological benefits acquired during the year of fitness. This intention is compatible with previous studies where the majority of subjects were still training four years after study participation [44].

Body mass was preserved during the study. Some studies showed that fitness training might induce weight loss by increasing exercise induced energy expenditure, but the amount of weight loss appears to be lower than predicted [45]. Possible explanations are a compensatory increase in energy intake or a reduction

Figure 5.2: Comparison of the change in maximal oxygen uptake ($\dot{V}O_{2\max}$ and walking cost over one year between a control group (N=10) and an intervention group (N=22). The whiskers represent standard deviations. * $p < 0.05$, two-way repeated measures ANOVA of the interaction between the effects of time and group.

of non-exercise energy expenditure [46]. In this study changes in body mass would have created a potential confounding factor and therefore no dietary indications were given to the subjects. As a result subjects remained weight stable during the study. Although body mass remained constant, FFM had the tendency to increase in the intervention group but significance was not reached ($p=0.06$). The increase in FFM was non-significant, possibly because the fitness training was of moderate intensity as previously shown in a similar multicomponent fitness training of moderate intensity [31].

$\dot{V}O_{2\max}$ increased by 1.3 ml/kg/min in the training group, whereas it declined by 1.8 ml/kg/min in the control group. The increase confirms previous studies showing that fitness training improves aerobic capacity [44]. Although one main determinant of $\dot{V}O_{2\max}$ is body mass, the effect of fitness training remained significant when presented in absolute terms (l/min). The training, and especially its endurance component, might have increased $\dot{V}O_{2\max}$ by acting on multiple physiological factors, which determine the age related decline in $\dot{V}O_{2\max}$. These factors include increased cardiac output, improved oxygen delivery to the muscle and increased oxidative capacity of skeletal muscles [47]. The observed increase in aerobic capacity indicates a good compliance to the intervention.

The cost of walking decreased by 0.13 ± 0.29 J/kg/m in the intervention group, compared to the control group in which the cost of walking increased by 0.12 ± 0.31 J/kg/m. A baseline cost of walking of about 2.4 J/kg/m is in line with the cost

of walking reported in previous studies [21, 48, 49]. One study has reported no changes in walking economy in older adults after a similar intervention [50]. In that study, the minimum cost of walking was around 0.15 ml O_2 /kg/m. Assuming a conversion factor of 20.3 J/ml O_2 for a regular diet [51], the minimum cost of walking in that study can be estimated at 3.05 J/kg/m, a very high value possibly indicating measurement bias. The results from the current study were in line with previous literature and indicate that multicomponent fitness training might delay the age-related decline in walking economy.

Increased metabolic efficiency during exercise might partly explain the effect of training on the metabolic cost of walking. Endurance training can influence subjects metabolism by decreasing energy expenditure during exercise [32]. Possible mechanisms include increased oxygen extraction and increased oxidative capacity of skeletal muscles. These physiological adaptations have been shown after enrolment in exercise training in patients with chronic heart failure and they might also contribute to increased aerobic capacity [52]. Other types of training such as task-specific motor learning interventions have been shown to be effective in improving motor control [53], with direct improvements in walking cost [54]. Task-specific interventions have relevant effects on walking economy but their effect on aerobic capacity is not significant. The current study instead involved a multicomponent fitness training and showed a significant effect both on walking economy and on aerobic capacity, which results in an increased energy reserve and is thought to have a positive influence on independence and quality of life [13].

Future studies could focus on the effect of multicomponent fitness training on independence and quality of life. The results of this study suggest that quality of life in trained older adults might have improved but no direct measures of quality of life were taken. Follow-up studies could assess whether the beneficial effect of multicomponent fitness training is maintained when the training is interrupted. It is also possible that a larger population or a longer period of training could reveal smaller but relevant consequences of multicomponent fitness training such as the trend shown for the fat-free mass in this study.

In conclusion, multicomponent fitness training improved aerobic capacity and decreased the metabolic cost of walking. Less energy needed for walking might promote sustained physical activity and contribute to prolong the independence of trained older adults from external aid for daily life activities.

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KRW and GV designed the study. GV collected the data, analysed the data and wrote the manuscript. KRW and AGB contributed to the interpretation of the data and reviewed the manuscript. The study was executed under supervision of KRW. Everyone who contributed significantly to the work has been listed, all authors read and approved the final manuscript.

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Chapter 6

DIURNAL PATTERNS OF PHYSICAL
ACTIVITY IN RELATION TO ACTIVITY
INDUCED ENERGY EXPENDITURE IN
OLDER ADULTS

VALENTI G, BONOMI AG, WESTERTERP KR

SUBMITTED FOR PUBLICATION.

Abstract

Background Ageing is associated with a declining physical activity level (PAL) and changes in the diurnal activity pattern. Changes in the activity pattern might explain the age-associated reduction of physical activity.

Objective The aim was to compare diurnal activity patterns in older subjects with a wide range of PAL.

Methods Thirty-one healthy subjects aged between 52 and 83y were recruited for the study. Subjects were divided in sedentary, moderately active, and active with energy expenditure measurements obtained with the doubly labelled water technique. Diurnal activity patterns were based on activity counts from an accelerometer during wake time and then divided in four quartiles of equal time length. Additionally, aerobic fitness was measured as maximal oxygen uptake.

Results Subjects had a PAL between 1.43 and 2.34 and a aerobic fitness between 18 and 49 ml/kg/min. Overall, activity patterns showed a peak in the first quartile of wake time (around 10 AM) followed by a gradual decline of, on average, 5% per hour. Active subjects reached their peak in the first quartile and remained active until after the third quartile (11% drop each quartile on average). Moderately active and sedentary subjects reached their peak during the second quartile with a decrease during the third quartile (respectively 29% and 17% drop each quartile on average). The drop in physical activity between the first and the second half of the wake time was negatively associated with aerobic fitness ($r=-0.39$, $p<0.05$).

Conclusion Active subjects maintained a larger amount of body movement for longer during their wake time. Diurnal physical activity declined more in older adults with lower aerobic fitness.

Introduction

Increasing age is accompanied by a gradual decline of physical activity and an increase in sedentary behaviour [1, 2]. A sedentary lifestyle in older adults is associated with several negative health outcomes such as disability [3], sarcopenia [4], diabetes, [5] cardiovascular diseases [6] and increased morbidity [7]. Therefore, the World Health Organisation sets specific goals of time spent in physical activity, namely 150 min/week in bouts longer than 10 minutes for individuals after the 65th year of age [8].

Objective assessments of physical activity level (PAL) in daily-living can be carried out by measuring total energy expenditure with the doubly labelled water technique (DLW) or by means of accelerometers [9]. The DLW is a highly accurate method to measure total energy expenditure and derive PAL in daily life [10]. The technique based on DLW provides the average PAL over the period of measure with no information about physical activity patterns. Accelerometers provide less accurate assessments of PAL than the DLW technique, but they preserve the information on activity patterns [9]. Therefore, combining measurements of PAL from DLW with activity patterns as provided by accelerometers can reveal differences in activity patterns between subjects with different PAL.

Diurnal activity patterns have been objectively characterised before to describe how physical activity is distributed during the day. Physical activity reaches a peak between 10 and 11 AM, after which it declines, allowing a gradual increase in sedentary behaviours[11, 12]. It has been therefore suggested that prolonging active morning bouts of physical activity could contrast the decline in physical activity and it might be an effective strategy to maintain higher PAL [11]. However, studies about physical activity patterns have never classified subjects according to their energy-expenditure derived PAL and there is no evidence so far that subjects with higher PAL are less prone to the diurnal decline in physical activity.

Increasing age and reduced physical activity are associated with declining aerobic fitness [13, 14], measured as maximal aerobic capacity of an individual [15, 16]. Aerobic fitness has been described both as a determinant and as an outcome of physical activity [17]. Aerobic fitness can determine physical activity; subjects with a low aerobic capacity are more prone to fatigue [18, 19] and their endurance is compromised [20]. Increased fatigue reported in unfit individuals might discourage them from being physical active, especially later in the day. At the same time, physical activity interventions such as endurance training [21] or lifestyle interventions [22] have been shown to increase aerobic capacity, indicating that improved aerobic fitness is one of the outcomes of increased physical activity. Thus, aerobic fitness is a potential covariate in studies concerning physical activity. Previous studies where aerobic fitness and physical activity were measured have

not discriminated physical activity by time of the day, thus the relationship between aerobic fitness and diurnal activity patterns has not been reported yet.

The design of intervention strategies for increasing physical activity to promote healthy ageing might benefit from more insights into how diurnal activity pattern characterises older adults with a higher PAL. The aim of the study was to compare diurnal activity patterns in older subjects with a wide range of PAL.

Methods

Population Thirty-one healthy subjects (15 males and 16 females) aged between 52 and 83 years (body mass index (BMI) 25.7 ± 2.1 kg/m²) were recruited by advertisements in local newspapers (Table 6.1). Respondents signed a written informed consent and completed a questionnaire including orthopaedic conditions, neurological disorders and cardiovascular problems. A doctor discussed the questionnaire with the respondents during a medical visit. All subjects were in good orthopaedic, neurological and cardiovascular conditions and were included. The study was conducted according to the Declaration of Helsinki and the Ethics Committee of the Maastricht University Medical Center approved the study. This trial was registered at www.clinicaltrials.gov as NCT01609764.

Table 6.1: Subject characteristics for each physical activity level group. Mean $\pm$ standard deviation (SD)

	Sedentary	Moderately Active	Active	Total
N	9	11	11	31
Gender (M/F)	2/7	7/4	6/5	15/16
Body mass (kg)	73 $\pm$ 9	77 $\pm$ 11	73 $\pm$ 13	74 $\pm$ 11
BMI (kg/m ²)	26.2 $\pm$ 1.5	25.9 $\pm$ 1.9	25.1 $\pm$ 2.7	25.7 $\pm$ 2.1
Age (y)	67 $\pm$ 8	65 $\pm$ 5	61 $\pm$ 6	64 $\pm$ 6
PAL	1.62 $\pm$ 0.09*	1.82 $\pm$ 0.04†	2.03 $\pm$ 0.14*†	1.84 $\pm$ 0.19
Activity (kCounts/d)	5.3 $\pm$ 1.6	6.0 $\pm$ 0.5	7.0 $\pm$ 1.6†	6.2 $\pm$ 1.4
$\dot{V}O_{2\max}$ (ml/min/kg)	25 $\pm$ 5	30 $\pm$ 6	32 $\pm$ 9†	29 $\pm$ 7
Wake time (h/d)	15.5 $\pm$ 1.0	16.0 $\pm$ 1.0	15.9 $\pm$ 0.9	15.9 $\pm$ 1.0
Sleep time (h/d)	8.5 $\pm$ 1.0	8.0 $\pm$ 1.0	8.1 $\pm$ 0.9	8.1 $\pm$ 1.0

Abbreviations: BMI, body mass index; PAL, physical activity level; $\dot{V}O_{2\max}$, maximal oxygen uptake per unit of body mass; *, $p < 0.05$ compared to the moderately active group; †, $p < 0.05$ compared to the sedentary group.

Study design Basal metabolic rate was measured on the first morning. Subsequently, free-living energy expenditure was measured during 2 weeks in daily-life. Physical activity was monitored simultaneously with an accelerometer, and subjects reported wakeup and sleep times in a diary. Aerobic fitness was measured at least two days before or after the physical activity measurement.

Energy expenditure Basal metabolic rate (BMR) was measured during 30 minutes under a ventilated hood in the supine position under standard conditions of rest, fasting, immobility, thermoneutrality and mental relaxation [23]. O_2 and CO_2 production sampled from the hood were measured with an indirect calorimeter (Omnical, Maastricht Instruments, Maastricht, The Netherlands). BMR was calculated from O_2 consumption and CO_2 production with Brouwer's formula [24].

Total energy expenditure (TEE) was measured using doubly labelled water, as previously described [25]. Briefly, after the collection of a baseline urine sample on the evening of day 0, subjects drank a weighted amount of $^2H_2^{18}O$. The dose resulted in a body water enrichment of about 120 p.p.m. for ^2H and about 240 p.p.m. for ^{18}O . Urine samples were collected from the second voiding in the mornings of days 1, 8 and 15, and in the evenings of days 1, 7 and 14. Urine samples were analysed with an isotope ratio mass spectrometer (Optima; VG Isogas, Middlewich, Cheshire, UK). Carbon dioxide production was calculated from the difference between the elimination rates of ^2H and ^{18}O . Total daily energy expenditure was calculated from carbon dioxide production, assuming a respiratory quotient of 0.85 [26].

Physical activity Subjects wore a tri-axial accelerometer (GT3X+, Acti-Graph, Pensacola, FL) on the lower back using a belt, as described before [27]. Accelerometer data were exported to Matlab (Mathworks, Natick, MA) and divided in epochs of 5 seconds. Counts were calculated by integrating body accelerations of each epoch after detrending and rectification of the signal from each axis. Activity counts were then integrated in epochs of one minute. Days during which data were missing or subjects carried the accelerometer for less than 10 hours were excluded and the average was calculated on the remaining data, assuming that daily physical activity is an ergodic process. Average counts per day were calculated over the days of measurement. Physical activity level (PAL) was then calculated as ratio between TEE and BMR.

Diurnal Activity Patterns Activity counts per minute were aligned according to time of the day. Mean counts over corresponding time intervals of the day for each subject were calculated to create a personalised activity pattern. The diurnal activity pattern was the activity pattern between the average wake up

time and the average to-bed time of the subject as derived from the diaries (Wake time). Subsequently, wake time was divided in four quartiles of equal time length. Activity levels of consecutive quartiles were compared to identify diurnal patterns. The first two quartiles and the last two quartiles were averaged to represent the physical activity of the first and the second half of the day. The difference in physical activity between the first and the second half of the day was a measure of the diurnal drop in physical activity. Sleep time was the time between the individual average to-bed time and average wake up time.

Aerobic fitness Aerobic fitness was measured as maximal oxygen uptake ($\dot{V}O_{2\max}$) during an incremental protocol on a cycle ergometer [28]. After a five-minutes warming up at a workload of 75W for men and 50W for women, the workload was increased by 50 W every 2.5 min. When the respiratory exchange ratio was higher than one or when heart rate reached a value of 35 bpm below the age-predicted maximal heart-rate ($220 \text{ bpm} - \text{age}$), the increase in workload was reduced to 25 W until exhaustion. Expired air was collected with a mask covering mouth and nose to be continuously analysed for O_2 consumption (Omnical, Maastricht Instruments, Maastricht, The Netherlands). $\dot{V}O_{2\max}$ was adjusted for body mass.

Data analysis The group was divided in subgroups according to PAL or age. The classification based on PAL defined subgroups of sedentary ($\text{PAL} < 1.75$) moderately active ($1.75 < \text{PAL} < 1.90$) and active subjects ($\text{PAL} > 1.90$). The classification based on age defined subgroups of younger ($\text{Age} < 62 \text{ y}$), middle ($62 < \text{Age} < 66 \text{ y}$) and older ($\text{Age} > 66 \text{ y}$) aged subjects. Diurnal activity patterns were derived in each subgroup. The Pearson correlation coefficient (r) and the coefficient of determination (r^2) were used to describe the association between the diurnal drop in physical activity and aerobic fitness or sleep time. All variables were expressed as mean $\pm$ standard deviation (SD). The statistical significance threshold was set at $p < 0.05$.

Results

Subjects had a PAL between 1.43 and 2.34 (mean $\pm$ SD, 1.84 ± 0.19) and an aerobic fitness between 18 and 49 ml/kg/min (mean $\pm$ SD, $29 \pm 7 \text{ ml/kg/min}$). Men were fitter than women (33 ± 8 vs. $26 \pm 4 \text{ ml/kg/min}$) but with similar PAL, age and wake time. Younger subjects ($N=10$, 5 males, $\dot{V}O_{2\max} = 33 \pm 6 \text{ ml/kg/min}$) were fitter than older subjects ($N=11$, 3 males, $\dot{V}O_{2\max} = 23 \pm 4 \text{ ml/kg/min}$), but with similar PAL and wake time. Sedentary, moderately active and active subjects did not differ in age or wake time but the active group was fitter than the sedentary one (Table 6.1).

The 24-hours activity pattern of the group showed a peak of activity in the morning with a subsequent gradual decrease of about 5% per hour (Figure 6.1). All groups reported similar wakeup and sleep times. Quartiles were therefore similar in all groups and went from around 8:00 to around 12:00 (quartile 1, Q1), from around 12:00 to around 16:00 (quartile 2, Q2), from around 16:00 to around 20:00 (quartile 3, Q3), and from around 20:00 to around 00:00 (quartile 4, Q4).

Figure 6.1: Diurnal physical activity pattern in older subjects (N=31)

Active subjects reached their peak of activity in Q1, which was maintained until and including Q3 (Figure 6.2). On average, the activity in this group declined by 11% every quartile. Moderately active and sedentary subjects reached their peak during the Q2 with a significant decrease during Q3 (respectively 29% and 17% drop each quartile). Younger subjects showed patterns similar to active subjects. Conversely, older subjects showed patterns comparable to the sedentary group (Figure 6.3).

Fitter subjects showed smaller drops in physical activity between the first and the second half of the day ($r=-0.39, p<0.05$) (Figure 6.4). Aerobic fitness, the drop in physical activity, and PAL were not related to wake or sleep time ($p>0.5$).

Figure 6.2: **Diurnal activity patterns in sedentary (N=9, PAL<1.75), moderately active (N=11, 1.75<PAL<1.90) and active (N=11, PAL>1.90) older subjects.** PAL, physical activity level as predicted from daily activity counts; Q1, first quartile of diurnal activity; Q2, second quartile of diurnal activity; Q3, third quartile of diurnal activity; Q4, fourth quartile of diurnal activity; +, outlier; *, $p<0.05$ compared to the previous quartile; **, $p<0.005$ compared to the previous quartile; ***, $p<0.001$ compared to the previous quartile.

Discussion

This study provides the first evidence that older subjects with a lower physical activity level showed a more abrupt drop in physical activity in the afternoon, compared to younger adults. Individuals with a more pronounced drop tended to be aerobically less fit.

The PAL range measured in the population of the study was 1.43 to 2.34. Similar PAL ranges are rarely reported in the literature where older subjects rarely show PAL higher than 2.00 [29, 30]. Due to the very active individuals in the group, the population in this study had not only a broad PAL but was also on average very active compared to previous studies [31]. Similarly, the range of aerobic fitness was broader than previous studies [32] and on average subjects were fitter than reported in previous studies, where the average aerobic fitness was around 24ml/kg/min [29]. Although high levels of physical activity and fitness might not be representative for a population of older adults, the broad ranges found in this population allowed the statistical power to compare the diurnal activity patterns between active and sedentary as well as fit and unfit older individuals.

The diurnal activity pattern of the whole group showed a peak around 10 AM followed by a progressive decline (Figure 6.1). This behaviour has been shown before in older individuals, where physical activity declined after a peak between 10 and 11 AM to give way to more sedentary behaviours [11, 12]. Comparing the patterns between active and sedentary subjects, active subjects had an earlier

Figure 6.3: **Diurnal activity patterns in younger (N=10, Age<62y), middle (N=10, 62<Age<66y) and older (N=11, Age>66) older subjects.** Q1, first quartile of diurnal activity; Q2, second quartile of diurnal activity; Q3, third quartile of diurnal activity; Q4, fourth quartile of diurnal activity; +, outlier; *, $p<0.05$ compared to the previous quartile; **, $p<0.005$ compared to the previous quartile; ***, $p<0.001$ compared to the previous quartile.

peak and sustained their activity level later in the day up to and including the third quartile (16:00–20:00 ca.). These results suggest that older subjects might achieve increased PAL by prolonging active morning bouts of physical activity [11].

One possible explanation for the decrease in physical activity in older adults during wake time is retirement [12]. In the Netherlands, individuals older than 65 years are mostly retired and this might induce a more sedentary lifestyle. However, physical activity declined in all age groups towards the end of wake time (Figure 6.3). Thus, retirement cannot be the only explanation for the diurnal decline in physical activity. Other explanations include lower aerobic fitness, which is associated with increased fatigue and might affect activity patterns [11, 33]. In the current study, the younger group was fitter than the older group and fitter individuals showed a smaller diurnal decline in physical activity (Figure 6.4). Thus a decrease in physical activity during wake time is mainly determined by aerobic fitness.

The results of the study are based on the division of the diurnal activity pattern in quartiles. A similar method has been proposed before in a study where the physical activity measured during 24 hours was divided in six intervals of four hours starting at fixed times of the day [34]. The method used in that study did not take into account possible shifts in the activity patterns due to individual characteristics such as the chronotype of subjects [35], work shifts, etc. To correct for these individual differences, the current study proposed a division in quartiles based on subjects' specific wakeup and to-bed time. This method is applicable only when potential shifts in the activity pattern is a confounding factor rather than an outcome. Wakeup and to-bed times were not significantly

Figure 6.4: **Drop in physical activity between the first and the second half of the day as a function of aerobic fitness in older subjects.** Aerobic fitness, maximal oxygen intake per kilogram of body mass, r^2 , coefficient of determination.

different between the groups here described, wake and sleep time did not correlate with fitness or the drop in physical activity and the potential shifts in activity patterns were not an outcome of the study. Therefore the division of the diurnal activity pattern in quartiles proposed is applicable to this study.

This study shows significant drops in physical activity in the third and fourth quartile of diurnal activity, in spite of the variability of the data. The data presented in Figure 6.2 and Figure 6.3 shows different degrees of variability in physical activity between groups and quartiles. Future studies including a larger population might provide more detailed results and define whether the variability is a characteristic of the group and quartile or it is due to possible outliers in the population.

Aerobic fitness was shown to be associated with the age-related changes in diurnal activity patterns. However, other physiological factors can be suggested and investigated. In particular altered levels of hormones such as melatonin [36] and cortisol [37] have been reported in individuals with disrupted diurnal patterns, typical of ageing. Both melatonin [36] and cortisol [38] are related to sleep and activity cycles and the disruption of their daily cycle could have a direct effect on diurnal activity patterns. Furthermore, aerobic fitness has been shown to reduce levels of cortisol [39] and increase melatonin in the blood [40]. The

study of diurnal activity patterns in subjects with different hormonal profiles could provide further insight into the age-related decline in physical activity and help the development of more effective intervention strategies.

In conclusion, this is the first study to report that active subjects maintain a larger amount of body movement for longer during their wake time. Diurnal physical activity declines more in older adults with lower aerobic fitness. Therefore higher physical activity level might be promoted by prolonging active morning bouts of physical activity and by increasing aerobic fitness.

Author contributions

KRW and GV designed the study. GV collected the data, analysed the data and wrote the manuscript. KRW and AGB contributed to the interpretation of the data and reviewed the manuscript. The study was executed under supervision of KRW.

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Chapter 7

QUALITY SLEEP IS ASSOCIATED WITH OVERNIGHT METABOLIC RATE IN HEALTHY OLDER ADULTS

VALENTI G, BONOMI AG, WESTERTERP KR

SUBMITTED FOR PUBLICATION.

Abstract

Background Increasing age is associated with an increase in overnight metabolic rate.

Objective To determine the relationship between quality sleep, sleep efficiency and overnight metabolic rate as measured in a respiration chamber in older subjects.

Methods The study design was cross-sectional. Forty subjects, aged 50 to 83 years (17 males, age 63 ± 7 y, BMI 25.7 ± 2.3 kg/m²) spent one night in a respiration chamber to measure sleep stages by polysomnography, and overnight metabolic rate (OMR). Data was collected between 23:00 and 07:00. Subsequently basal metabolic rate (BMR) was measured under a ventilated hood. Quality sleep was calculated as time spent in rapid-eye movement (REM) sleep and slow wave sleep divided by total sleep time, and sleep efficiency was calculated as total sleep time divided by the sleep period time. Body movement was measured between 23:00 and 07:00 with an accelerometer on the wrist. Overnight metabolic rate was adjusted for body size by dividing by basal metabolic rate (OMR/BMR).

Results OMR/BMR was positively associated with age ($r=0.48$, $p<0.001$), and quality sleep was negatively associated with age ($r=-0.51$, $p<0.001$). The variance of OMR/BMR was significantly explained by quality sleep ($r=-0.58$, $p<0.001$). Body movement was negatively related to sleep efficiency ($r=-0.38$, $p<0.01$) with no effect on OMR/BMR. When OMR/BMR was adjusted for quality sleep, the effect of age was non significant.

Conclusion Quality sleep is inversely associated with the age related rise in overnight metabolic rate, suggesting that increased overnight metabolic rate is a biological sign of ageing as a consequence of diminished quality sleep.

Introduction

Sleep is a temporary state of altered consciousness that occurs for approximately one third of human life. Sleep promotes growth, recovery and cognitive well-being. Reduced total sleep time (TST) affects endocrine and metabolic functions and sleep-deprived subjects can show confusion, depression, hallucinations and in extreme cases death [1–9]. During sleep, slow wave sleep (SWS) is the stage associated with growth and recovery [10]. Rapid-eye movement (REM) is associated with cognitive functions and its selective deprivation is associated with executive functions, pain threshold and emotional memory consolidation [11–13]. Studies that selectively deprived subjects of SWS or REM showed a rebound effect during the period following the deprivation, underlying the importance of both SWS and REM.

Ageing is associated with a reduction of TST, REM and SWS. After 30 years of age wake time after sleep onset increases 10 minutes per decade, reducing sleep time between sleep onset and final awakening, known as sleep efficiency, from 95% in young adults to less than 80% in older adults [14, 15]. Similarly, quality sleep, defined as the sum of rapid REM and SWS, progressively decreases from 60% of TST in children to 20% in old adults [14, 15]. Older individuals also show a reduction of basal metabolic rate (BMR) with age, while overnight metabolic rate (OMR) is preserved or increased. The reduction in BMR is a sign of decreased fat-free mass and it had been assumed that OMR would proxy this trend and decrease with age. On the contrary, previous studies showed that overnight metabolic rate is lower than BMR in 11 years old children, similar to BMR in 25 years old adults, and higher than BMR in 61 years old subjects [16]. Changes in quality sleep or sleep efficiency have possible consequences for overnight metabolic rate, which would indicate that OMR is a biological sign of ageing.

Possible explanations for an increased OMR in older individuals include less quality sleep and decreased sleep efficiency. Some studies observed a lower metabolic rate during quality sleep, particularly SWS [17–19]. Older adults spend less time in quality sleep and this could contribute to higher OMR. Additionally, body movement is reduced during sleep time [20]. Older adults with lower sleep efficiency spend more time awake and are more likely to move during the night with a consequent increase in OMR [21, 22].

This study aimed at determining the relationship between quality sleep, sleep efficiency and metabolic rate in older subjects staying overnight in a respiration chamber. Sleep was assessed with polysomnography to determine sleep and wakefulness time as well as to allow the distinction between different sleep stages. Body movement was assessed simultaneously with actigraphy. The respiration chamber allowed the assessment of OMR, followed by measurement of BMR

under a ventilated hood [16].

Methods

Population Subjects were 17 men and 23 women, aged 50 to 83, 63 ± 7 years, recruited by advertisements in local newspapers (Table 7.1). They underwent a medical screening including measurement of body weight and height and the completion of a questionnaire related to health, use of medication, physical activity, alcohol consumption, smoking and sleeping behaviour. Good health was required for inclusion, whilst exclusion criteria were medications, sleep complaints, smoking, or heavy drinking. All subjects included in the study were in good health, not taking medication, nonsmokers, at most moderate alcohol consumers, and with no complaint of sleep disorders such as sleep apnea. The study was conducted according to the Declaration of Helsinki and the Ethics Committee of the Maastricht University Medical Center approved the study. The trial was registered at www.clinicaltrials.gov as NCT01609764.

Table 7.1: Subject characteristics. Mean $\pm$ SD

Gender (m/f)	17/23
Age (y)	63 $\pm$ 7
Height (m)	1.69 $\pm$ 0.10
Body Mass (kg)	73.4 $\pm$ 9.9
BMI (kg/m ²)	25.7 $\pm$ 2.3
BMR (kJ/min)	4.4 $\pm$ 0.6
OMR (kJ/min)	4.6 $\pm$ 0.7
OMR/BMR	1.06 $\pm$ 0.06
Body movement (counts/min)	276 $\pm$ 162
VAS sleep score (%)	63 $\pm$ 18

Abbreviations: BMI, Body mass index; BMR, basal metabolic rate;
OMR, overnight metabolic rate; VAS sleep score, visual analogue scale
sleep score.

Study design On the day of the experiment, subjects arrived at the university at 19:00. Electrodes for polysomnographic measurements were applied and a triaxial accelerometer was placed on the right wrist. At 21:00, subjects entered a respiration chamber and were instructed to sleep between 23:00 and 07:00. Basal metabolic rate (BMR) was measured directly after leaving the respiration chamber between 07:00 and 08:00 and before any consumption of any food or beverage. At the end of the visit, subjects were asked to evaluate how good they

had slept using a VAS consisting of a 10 cm line marked from 0 (very bad) to 100% (very good).

Polysomnography Polysomnographic recordings were obtained between 23:00 and 07:00 with a digital electroencephalogram system (BrainRT, OSG BVBA, Rumst, Belgium). Electrodes for electroencephalogram, bilateral electrooculograms, and submental electromyograms were applied according to standardised criteria [23–27]. Sleep records were visually scored in 30s–epochs by an experienced researcher following the standard guidelines [23–27]. Stages included awake, REM sleep, non–REM sleep stage 1, non–REM sleep stage 2 and SWS. Sleep period time was defined as the time between sleep onset and last awaking, including wake time after sleep onset. TST was defined as the time between sleep onset and last awaking, excluding wake time after sleep onset. Body movement during the night was monitored with a triaxial accelerometer (GT3X+, ActiGraph LLC, Pensacola, FL) on the right wrist.

Energy expenditure OMR was measured in a respiration chamber. The respiration chamber is an airtight room sized 18m³ and equipped with a bed, table, chair, freeze toilet, washing bowl and television. During the stay in the respiration chamber, O₂ consumption and CO₂ production were measured according to the protocol used in previous studies [26–28]. Basal metabolic rate was measured for 30 minutes under a ventilated hood [29] in the supine position under standard conditions of wake, rest, fasting, immobility, thermoneutrality and mental relaxation.

Data analysis Quality sleep was calculated as time spent in REM sleep and SWS divided by TST, and sleep efficiency was calculated as TST divided by the sleep period time. Body movement was calculated from the accelerometer as activity counts averaged between 23:00 and 07:00. Calculation of metabolic rate from measured oxygen consumption and carbon dioxide production was based on Brouwer’s formula [30]. OMR was calculated as the average energy expenditure between 23:00 and 07:00. BMR was calculated as the average energy expenditure during the last 20 minutes under the ventilated hood. To adjust for body size, OMR was divided by BMR (OMR/BMR) [16, 31].

Statistical analysis Pearson product–moment correlation coefficient (*r*) was used to quantify associations between variables. All variables were expressed as mean±standard deviation (SD). The significance threshold was set to *p*<0.05.

Results

A typical example of chronological display of the sleep stages (hypnogram) is presented in Figure 7.1, aligned with energy expenditure and body movement. Sleep period time was on average 434 ± 67 min, wake time after sleep onset was 64 ± 50 min and TST was 370 ± 84 min. Sleep efficiency was $85 \pm 13\%$ (Table 7.2). Quality sleep was $41 \pm 10\%$ of the TST; 69 ± 26 min was spent in REM ($18 \pm 6\%$ of TST) and 84 ± 37 min in SWS ($23 \pm 9\%$ of TST). OMR was on average 4.6 ± 0.7 kJ/min and BMR was 4.4 ± 0.6 kJ/min resulting in an OMR/BMR of 1.06 ± 0.06 (Table 7.1 and Table 7.2).

Figure 7.1: **Polysomnographic hypnogram of a typical subject, aligned to energy expenditure and body movement.** REM, rapid eye movement sleep; N1, non-REM sleep stage 1; N2, non-REM sleep stage 2; SWS, slow wave sleep.

OMR/BMR was positively associated with age ($r=0.48$, $p<0.001$) and quality sleep was negatively associated with age ($r=-0.51$, $p<0.001$) (Table 7.3). The variance of OMR/BMR was partly explained by quality sleep ($r=-0.58$, $p<0.001$) (Figure 7.2). Body movement was negatively related to sleep efficiency ($r=-0.38$, $p<0.01$) with no effect on OMR/BMR (Table 7.3).

When OMR/BMR was adjusted for quality sleep, the association with age was non significant ($r=0.24$). Sleep scores from the visual analogue scale were negatively associated with age ($r=-0.40$, $p<0.01$) and OMR/BMR ($r=-0.35$, $p<0.05$) and were related to both quality sleep ($r=0.44$, $p<0.01$) and sleep

Table 7.2: Duration of sleep-related variables overnight. Mean $\pm$ SD

Sleep period time (min)	434 $\pm$ 67
WASO (min)	64 $\pm$ 50
TST (min)	370 $\pm$ 84
N1 (min)	46 $\pm$ 27
N2 (min)	173 $\pm$ 58
REM (min)	69 $\pm$ 26
SWS (min)	83 $\pm$ 37
Quality sleep (%)	41 $\pm$ 10
Sleep Efficiency (%)	85 $\pm$ 13

Abbreviations: Sleep period time, time between sleep onset and the final awakening; WASO, wake after sleep onset; TST, total sleep time; N1, non-REM sleep stage 1; N2, non-REM sleep stage 2; REM, rapid eye movement sleep; SWS, slow wave sleep.

Table 7.3: Correlation matrix between age, OMR/BMR, sleep-related variables, body movement and visual analog scale sleep score

	OMR/BMR	QS	SE	Body movement	VAS sleep score
Age	0.48***	-0.51***	-0.26	0.02	-0.40**
QS	-0.58***	—	0.15	-0.02	0.44**
SE	-0.16	0.15	—	-0.38**	0.41**

Abbreviations: OMR/BMR, overnight metabolic rate divided by basal metabolic rate; QS, quality sleep; SE, sleep efficiency; VAS sleep score, visual analogue scale sleep score; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

efficiency ($r=0.41$, $p < 0.01$).

Discussion

This study demonstrated for the first time that quality sleep was inversely associated with the age related rise in OMR/BMR and when OMR/BMR was adjusted for quality sleep, the effect of age was non significant. Body movement increased with reduced sleep efficiency with no consequence for OMR/BMR.

On average, quality sleep was 41 $\pm$ 10% of TST. Quality sleep was negatively associated with age. This is in line with previous observations. In a study on 2685 subjects aged 62 $\pm$ 11 y, quality sleep was about 38% of TST [32]. The same

Figure 7.2: **Correlations between overnight metabolic rate and age, and overnight metabolic rate and quality sleep.** OMR/BMR, overnight metabolic rate divided by basal metabolic rate; r , Pearson product-moment correlation coefficient.

study reported that quality sleep was significantly reduced in subjects older than 61 y, compared to younger adults. Similar results were shown previously for smaller groups [33–35]. In addition, OMR was on average 4.7 kJ/min, which is comparable to previous measures in older adults where OMR was on average 4.6 kJ/min [16].

Overnight metabolic rate was on average 6% higher than BMR and increased with age; subjects in their sixth decade showed similar OMR and BMR, while in subjects in their eighth decade OMR was around 10% higher than BMR. Previous studies showed that overnight metabolic rate is similar to BMR in young adults [16, 18, 21, 36]. Some studies also showed that OMR/BMR is lower in children, and higher in old adults [16, 37]. Our results suggest that this is partly determined by diminished quality sleep. When OMR/BMR was adjusted for

quality sleep, the effect of age was non significant, indicating that the increase of OMR/BMR with age is mediated by quality sleep and that there is no direct effect of age on OMR/BMR.

This study showed that lower OMR/BMR is associated with more quality sleep. This result is consistent with previous studies where quality sleep, particularly SWS, was associated with a reduction of metabolic rate of 2 to 3% [17–19]. While some studies report that this reduction is non-significant, SWS is consistently reported as the stage with the lowest metabolic rate, often followed by REM [27, 38, 39], especially in comparison with WASO [27]. The association between OMR/BMR and quality sleep supports the hypothesis that metabolic rate decreases during quality sleep relative to increases during WASO. One possible mechanism to explain increased OMR/BMR and decreased quality sleep with increasing age is altered autonomic regulation. Autonomic regulation is responsible for regulating physiological parameters such as blood pressure, which is typically elevated in older adults. High blood pressure overnight has been associated with diminished sleep quality and altered sleep duration [40] and could result in increased OMR. Thus increased OMR/BMR might be one of the signs of age-related alterations of autonomic regulation.

Reduced sleep efficiency has been previously suggested as an explanation for the increased OMR/BMR in older individuals [16]. Ageing reduces sleep efficiency and increases time spent awake during the night [15]. Time spent awake is associated with increased body movement and thus increased metabolic rate [21, 22]. In the population of this study, increased body movement was associated with lower sleep efficiency, but with no effect on OMR/BMR. Overnight body movement intervals were short and the increase in metabolic rate was possibly too short to significantly increase OMR. Furthermore, sleep efficiency in this population was higher than previously reported in older adults [14, 32, 41]. Increased sleep efficiency could have reduced the effect of ageing, hence the correlation between sleep efficiency and age was not significant. Similar studies in populations of less efficient sleepers could reveal whether sleep efficiency and body movement are mediators between age and OMR/BMR, together with quality sleep.

Changes in sleep architecture have been related to ageing but this is the first study to associate these changes with overnight metabolic rate [14, 15]. Results show not only that both quality sleep and OMR/BMR increase with age, but also that quality sleep and OMR/BMR are related to each other. This suggests that increased OMR/BMR is a biological sign of ageing as a consequence of diminished quality sleep. The association of increased OMR/BMR with adverse outcomes needs further studies.

One limitation of this study is that all subjects were healthy and the effect of age-related conditions was not explored. Among these conditions, breathing disorders, such as sleep apnea, high blood pressure, and dementia are associated

with decreased sleep and quality sleep and might further increase OMR/BMR in older individuals. Additionally, the high sleep efficiency measured in this population might have reduced the effect of ageing on OMR/BMR, thus limiting the conclusion drawn from the results.

In conclusion, quality sleep is inversely associated with the age related rise in overnight metabolic rate, suggesting that increased overnight metabolic rate is a biological sign of ageing as a consequence of diminished quality sleep.

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KRW and GV designed the study. GV collected the data, analysed the data and wrote the manuscript. KRW and AGB contributed to the interpretation of the data and reviewed the manuscript. The study was executed under supervision of KRW.

Everyone who contributed significantly to the work has been listed, all authors read and approved the final manuscript.

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Chapter 8

DISCUSSION

The research presented in this thesis aimed at providing insights into physical activity in older adults, with a focus on walking economy and circadian pattern. Physical activity was monitored with a tri-axial accelerometer for movement registration. The validity of accelerometers to objectively monitor physical activity was firstly generalised from lean subjects to overweight and obese subjects. The adoption of a validated accelerometer and an activity recognition algorithm showed that walking activities were a major contributor to physical activity. Walking was shown to be a higher intensity activity for older adults. Beyond energy expenditure, accelerometry allowed to predict walking economy, measured as metabolic cost of walking. Walking cost was shown to increase with age and the increase was associated with gait rate and with body acceleration in the horizontal plane. Multicomponent fitness training decreased walking cost in older adults, preserving walking economy, indicating how training programs might delay mobility limitation with increasing age.

Physical activity and energy expenditure shows a circadian pattern. Physical activity peaks in the early morning, where sedentary individuals were more prone to sedentary behaviours in the afternoon than those with a higher physical activity level and a higher physical fitness. Older adults show a higher overnight metabolic rate than young adults. The increased overnight metabolic rate was independent of physical activity and was inversely associated with quality sleep.

Validity of accelerometry for physical activity monitoring

The assessment of physical activity is important for understanding relations between physical activity and health and for determining the effectiveness of lifestyle interventions [1]. Accelerometers are typically validated in lean subjects and can explain up to 60% of the variance in physical activity level in this population [2]. The results reported cannot be extended to populations with different characteristics before their generalisability is verified. Given the increase in body weight with age [3, 4], the prediction of physical activity level and activity energy expenditure from an accelerometer was cross-validated in a population of overweight and obese subjects (**Chapter 2**). Activity counts could explain 47% of the variance of the simultaneously doubly labelled water assessed physical activity level, in line with the validation in lean subjects [5]. The result was also comparable with a previous study in overweight individuals, reporting 45% of the variance in activity energy expenditure explained with an accelerometer [5–7]. Thus a doubly labelled water validated accelerometer can be used to assess physical activity in subjects with a higher body mass index like older adults.

Walking as a contributor to physical activity

Insights into physical activity types might reveal strategies to promote physical activity. Activity recognition algorithms have been previously applied to identify different types of activity using the acceleration signal recorded with only one accelerometer [8]. Here, an activity recognition algorithm was developed and applied to free-living data to identify walking activity to determine the contribution of walking to physical activity in daily life (**Chapter 3**). Walking counts accounted for about 40% of total counts and were produced in about 20% of the activity time. Thus, ambulatory activities like walking were a major contributor to physical activity in older adults, although most of the activity time was spent in non-walking activities. Non-walking activity time was mainly spent in lower intensity activities such as deskwork, housekeeping, gardening or driving. The intensity of non-ambulatory activities was on average three times lower than walking activities. Older adults might have preferred low intensity activities rather than walking activities at high intensities with a possible negative effect on overall physical activity level [9, 10]. However, forms of locomotion other than walking such as biking or running and other activities such as housekeeping or gardening might have been occasionally conducted at higher intensities than walking. Given the low average intensity of non-ambulatory activities it can be concluded that high intensity activities in this population were limited.

Assessment of walking economy with an accelerometer

Quantifying activity intensity by means of activity counts per unit of time does not account for the metabolic economy of such activities. A measure of economy is given by the energy required to produce a given amount of external work. Walking economy or cost, for example, is defined as the steady-state energy expenditure for a given speed of walking. Whereas previous studies used activity counts to predict walking intensity, **Chapter 4** of this thesis describes a model to predict walking cost from different features extracted from body acceleration, namely step rate and measures of regularity of body acceleration. It was shown that increased step rate and the regularity of body acceleration in the horizontal plane (frontal and lateral axes) could explain 46% of the inter-individual variance in walking cost. This indicates that irregular body acceleration might be an indicator of walking instability [11] which occurs with increasing age and is shown to contribute to increased walking cost. Possible contributors to the remaining variance in walking cost are increased co-activation of antagonist muscles, as a result of decreased muscle strength, and decreased aerobic capacity, which is among the predictors of preferred walking speed [12]. Interventions targeting walking stability, muscle strength and aerobic capacity might indirectly reduce the cost of walking.

Effects of training on walking economy

The observed decrease in walking economy with increasing age might be delayed with exercise training, i.e. multicomponent fitness training. Multicomponent fitness training is a combination of resistance, stretching and endurance training [13, 14], providing subjects with the combined benefits of these training categories. Accordingly, results presented in **Chapter 5** showed that multicomponent fitness training decreased the energetic cost of walking in older adults. Comparing a training group and a control over a one-year interval, there was a significant interaction between the effects of time and group on walking economy and aerobic fitness, with an increase in the training group versus a decrease in the control group. Thus, training programs could delay the mobility limitation with increasing age by lowering the cost of walking and increasing aerobic capacity.

Alternative interventions for delaying mobility limitations include walking-specific motor learning. Subjects are asked to perform walking exercises aimed at increasing smoothness and coordination of movements of walking. The intervention was shown to be effective in improving motor control while walking [15], with a consequent reduction in walking cost [16], but the effect on aerobic capacity was not significant. The intervention described in this thesis showed a significant effect both on walking economy and on aerobic capacity, which is thought to have a more positive effect such as prolonging independent living.

Physical activity level and diurnal pattern

A study on the diurnal pattern of physical activity revealed that older adults are more inclined to sedentary behaviour in the afternoon [17]. To provide further insight into physical activity level and activity pattern, the diurnal pattern of physical activity was measured in older adults with a wide range physical activity levels (**Chapter 6**). The results revealed that physically active and fitter individuals maintained physically active for longer during the day, while subjects with lower activity level were more prone to sedentary behaviours in the afternoon. A higher and more sustained activity level in fitter individuals might be explained by a positive effect of fitness on physical activity or, the other way around, a higher activity level inducing a higher fitness. Meijer et al. [10] showed moderate intensity exercise training resulted in an improved physical fitness in older adults but had no effect on total daily physical activity. Training activity was compensated for by a decrease in non-training physical activity, an observation in agreement with earlier findings [9, 18]. Compensation of training activity by a decrease in non-training physical activity seems to be typical for older adults. Trainings studies in younger adults resulted in an increase in physical activity without affecting non-training activity [19]. Interestingly, Meijer et al. [10] trained older subjects during the late afternoon and the decline

in non-training activity preceded the training sessions. The compensation in physical activity as a consequence of participation in exercise training was an anticipatory mechanism. Thus, exercise training did not induce a higher physical activity level in older adults despite a training induce increase in physical fitness

Circadian pattern of energy expenditure

Energy expenditure shows a clear circadian pattern, increasing in the morning after getting up and physically active, decreasing again when going asleep at night, reaching the lowest level at complete rest. Overnight metabolic rate (OMR) is close to maintenance metabolism or basal metabolic rate (BMR). However, Adriaens et al. [20] showed OMR to be lower than BMR in 11 years old children, similar to BMR in 25 years old adults, and higher than BMR in 61 years old subjects. Results as presented in **Chapter 7** showed the higher OMR/BMR in older adults was associated with a lower prevalence of two sleep stages, namely rapid-eye movement (REM) sleep and deep sleep. Decreased REM sleep and deep sleep indicate decreased sleep quality [21], and the time spent in these two sleep stages was expressed as a percentage of sleep time. The incidence of quality sleep declined with age indicating that the amount of quality sleep declines with age. The association between quality sleep and OMR/BMR supports the suggestion by previous studies that metabolic rate decreases during quality sleep, especially during deep sleep [22, 23].

Ageing is associated with increasingly disrupted sleep, and older adults typically have short fragmented night sleep and frequent daytime napping [24, 25]. Sleep efficiency is a measure of this aspect of sleep, calculated as total sleep time as a percentage of the time between sleep onset and last awaking. An individual who, after falling asleep in the evening, remains asleep during the whole night until the next morning will show a sleep efficiency of 100%. An individual who experiences frequent awakenings with possibly long periods of wakes after sleep onset will show a lower value of sleep efficiency. Wake time is normally associated with activity and thus increases metabolic rate [26]. From these considerations it could be hypothesised that decreased sleep efficiency might be associated with increased body movement and consequently with higher OMR/BMR. Observations presented in **Chapter 7** confirmed subjects with lower sleep efficiency showed increased body movement, but neither sleep efficiency nor body movement were associated with OMR/BMR. One explanation could be that sleep efficiency might have been better than expected for this population of older adults, as shown by the relatively high average sleep efficiency and by the non-significant correlation of age with sleep efficiency and body movement. Thus, the associations shown in **Chapter 7** suggest overnight metabolic rate is a function of quality sleep rather than sleep efficiency related body movement.

Conclusions

- The validity of an accelerometer to assess physical activity in lean subjects can be generalised to overweight and obese subjects.
- Walking activities are a major contributor to physical activity in older adults.
- In older adults, walking is a relatively high intensity type of physical activity.
- The age-associated decline in walking economy is associated with the adoption of an increased gait rate and with irregular body acceleration in the horizontal plane.
- Walking economy can be estimated with a waist-worn accelerometer from the regularity of body acceleration as deviation from a personalised template.
- Multicomponent fitness training improves aerobic capacity and walking economy in older adults
- Active older adults maintain higher activity levels for longer during their wake time.
- Quality sleep is inversely associated with the age related increase in overnight metabolic rate.

Directions for future research

Accelerometers can explain 40 to 60% of the inter-individual variance of physical activity level [27, 28]. Here, 47% of the variance could be explained by activity counts derived from an accelerometer. More accurate assessments of physical activity can be achieved by applying activity recognition algorithms [29]. The recognition of activities allows accounting for activity-specific associations between activity counts and physical activity level. For example, the walking recognition model described in this thesis provided a classification of activity counts to include in a multiple linear model. The explained variance of physical activity level after the recognition of walking increased to 58%. The recognition of different types of non-ambulatory activities will further improve the accuracy of the estimations of physical activity.

Activity recognition algorithms have the potential to provide insights into determinants of physical activity. About 40% of the activity counts described here are produced during walking activities. The detection of other types of activity in daily life, such as biking or shopping, can provide insight into additional determinants of physical activity in daily life. The results of such studies in different age groups can describe changes in determinants of physical activity

with increasing age. Furthermore, activity recognition models can be based on heuristic features to be defined by interpretable parameters. One example of a heuristic feature is the acceleration signal power, which is a measure of intensity of activity. Typically, acceleration signal power during running is higher than during walking and it can be included in a model to discriminate between such activities. The study of models that implement signal power as a parameter could provide information about the transition between walking and running. For example, a higher threshold of signal power between walking and running might be related to higher preferred transition speed, which is an outcome of energetic and biomechanical factors [30]. Thus, activity recognition models based on heuristic features could be characterised by parameters that are interpretable.

The estimation of walking economy from an accelerometer was validated in the laboratory, and the validity under free-living conditions is still to be verified. The advantage of estimating walking economy in daily life is that an unsupervised setting provides more representative data to describe features of human walking. Furthermore the use of an unobtrusive accelerometer allows monitoring changes in walking economy with time and under free-living conditions including possible early detection of age-related changes. For example, step rate and irregularity of body acceleration in the horizontal plane during walking as measured in older adults with a history of falls as compared to older adults with no history of falls, revealing possible associations between these features and fall risk.

Ageing was shown to be associated with a declining physical activity level and with changes in diurnal activity pattern. Diurnal physical activity declined more in subjects with lower aerobic fitness. The diurnal decline in physical activity was observed at all ages studied and became more pronounced at higher age. A suggestion for the study of metabolic determinants is the measurement of substrate oxidation and physical performance during exercise in relation to time of day. Skeletal muscle glycogen concentration, as a determinant of physical performance, shows a diurnal pattern [31]. The indicated procedure to further elucidate the role of aerobic fitness as a determinant of the diurnal decline in physical activity is an exercise training intervention.

The observed relation between body movement and sleep efficiency illustrates the potential of accelerometry for the prediction of sleep parameters. Ideas for additional parameters are heart rate and skin or core temperature. The study of overnight metabolic rate in subjects with an age-related decrease in sleep efficiency would reveal whether sleep disruption and body movement are mediators between age and OMR/BMR. Future studies could reveal whether increased OMR/BMR is associated with increased daytime sleepiness and decreased physical activity and propose intervention strategies to maintain quality sleep.

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SUMMARY

Physical activity represents a fundamental vital function, which declines after the age of 50 years. Lower physical activity level is associated with reduced mobility and higher mortality risk in older adults. Physical activity can be assessed wearing an accelerometer, a small device that measures accelerations and can monitor pattern, intensity and type of physical activity. Walking is the most common type of physical activity and its energetic cost increases with age, possibly contributing to the decline in physical activity.

Insights into physical activity in older adults with a focus on walking and circadian pattern can lead to knowledge on the age-related decline in physical activity and suggest strategies for intervention. Given the increase in body weight with age, the validity of accelerometers to objectively monitor physical activity was firstly generalised from lean subjects to overweight and obese subjects. A validated accelerometer was then used to describe the importance of walking in achieving higher levels of physical activity in older adults and to detect determinants of the energetic cost of walking. The effect of multicomponent fitness training on the energetic cost of walking in older adults was then determined. Finally, the effect of ageing on overnight metabolic rate and wake time activity patterns was studied.

Data from thirty-six overweight to obese subjects were analysed to generalise validity of accelerometers to objectively monitor physical activity. Subsequently, twenty-six untrained older adults, aged 50 to 83 years were recruited as training group to follow a one-year multicomponent fitness-training program. Results from the training group were compared with a control group of sixteen subjects, matching the training group for age, weight, body composition calculated from total body water, and fitness level measured as maximal oxygen uptake. Measurements took place at baseline and after one year. Free-living energy expenditure was measured in the intervention group to derive physical activity level. Physical activity was monitored over two weeks intervals with an accelerometer. An algorithm based on template matching and signal power was developed to classify activity counts as walking and non-walking counts. The accelerometer was also used to detect determinants of the energetic cost of walking on a treadmill, as measured with indirect calorimetry. Determinants of overnight metabolic rate in a respiration chamber were derived by simultaneously measuring sleep stages with a polysomnogram.

Activity counts in overweight to obese individuals could explain 47% of the variance of the physical activity level, in line with the validation in lean subjects. In older adults, walking counts accounted for about 40% of daily activity counts and were produced in about 20% of the activity time. Non-walking activity time was mainly spent in lower intensity activities. The variance in the energetic cost of walking could partly be explained by increased step rate and the regularity of body acceleration in the frontal and lateral axes. One-year multicomponent fitness training delayed the observed increase in walking cost associated with

increasing age. Analysis of the diurnal pattern of physical activity revealed that older adults with higher physical activity level and aerobic fitness maintained active for longer during the day, while subjects with lower activity level were more prone to sedentary behaviours in the afternoon. During the night, the relative increase in energy expenditure associated with increasing age was a function of a decrease in quality sleep rather than a decrease in sleep efficiency.

In conclusion, accelerometry is a valid technique to assess physical activity in individuals with increased body weight. In older adults, walking activities are a major contributor to physical activity and they occur at relatively higher intensity. Walking economy declines with increasing age and the decline is associated with the adoption of an increased gait rate and with irregular body acceleration in the horizontal plane. Multicomponent fitness training delays the age-related decline of walking economy. During their wake time active older adults maintain higher activity levels for longer. During the night, the age related increase in overnight metabolic rate is associated with less quality sleep rather than lower sleep efficiency with increased body movement.

SAMENVATTING

Lichamelijke activiteit is een fundamentele vitale functie die afneemt bij het ouder worden. Een lager lichamelijk activiteitsniveau is geassocieerd met een verminderde mobiliteit en een hoger sterfterisico op latere leeftijd. Lichamelijke activiteit kan worden bepaald door het dragen van een bewegingsmeter die lichaamsversnellingen meet en zo het patroon, de intensiteit en het type lichamelijke activiteit kan vastleggen. Lopen is de meest voorkomende vorm van lichamelijke activiteit en het energiegebruik voor lopen neemt toe bij veroudering. Dit draagt mogelijk bij aan de afname van de lichamelijke activiteit naarmate men ouder wordt.

Kennis over de lichamelijke activiteit van ouderen, wat betreft energiegebruik en activiteitspatroon, kan leiden tot kennis over de leeftijd gerelateerde daling van de lichamelijke activiteit. Ook kan dit inzicht nieuwe strategieën suggereren voor interventie. Allereerst werd een bewegingsmeter gevalideerd voor het meten van lichamelijke activiteit bij mensen met een hoger lichaamsgewicht zoals veel ouderen. De gevalideerde bewegingsmeter werd vervolgens gebruikt om bij ouderen het belang van lopen te bepalen, als determinant van de totale lichamelijke activiteit. Daarnaast werd op basis van lichaamsversnelling een maat ontwikkeld voor bewegingsefficiëntie tijdens lopen. Aansluitend deed een groep ouderen een jaar lang fitness training om na te gaan of hiermee het energiegebruik voor lopen kan worden verminderd. Als determinanten van het activiteitspatroon werden lichamelijke fitheid en de kwaliteit van slaap onderzocht.

De validatie van een bewegingsmeter voor het meten van lichamelijke activiteit bij mensen met een hoger lichaamsgewicht vond plaats bij 36 proefpersonen met overgewicht en obesitas. Het uiteindelijke onderzoek werd uitgevoerd bij 42 ongetrainde ouderen van 50 tot 83 jaar, 26 gerekruteerd als trainingsgroep om een jaar lang een fitness programma te volgen en 16 als controlegroep, overeenkomend wat betreft leeftijd, gewicht en lichaamssamenstelling. De metingen vonden plaats bij aanvang van de studie en na een jaar. Lichamelijke activiteit werd bepaald met de bewegingsmeter over twee aaneengesloten weken. De activiteit lopen werd geclassificeerd door ontwikkeling van een algoritme op basis van template matching en signaalsterkte. De maat voor bewegingsefficiëntie tijdens lopen werd ontwikkeld door proefpersonen met vier snelheden te laten lopen op een tredmolen, met gelijktijdige meting van lichaamsversnelling en energiegebruik. Determinanten van het activiteitspatroon werden bepaald door meting van lichamelijke fitheid als zuurstofopname bij maximale inspanning op een fietsergometer en meting van kwaliteit van slaap op basis van energiegebruik tijdens overnachting in een respiratiekamer met gelijktijdige analyse van slaapstadia met een polysomnogram.

Activiteitsmeting met de versnellingsopnemer kon ongeveer de helft van variatie in het energiegebruik voor lichamelijke activiteit verklaren bij proefpersonen met overgewicht en obesitas, een vergelijkbaar resultaat aan eerdere validatie bij personen met een normaal lichaamsgewicht. Bij ouderen werd ongeveer 20% van de actieve tijd besteed aan lopen en de bijdrage hiervan aan de totale dagelijkse

lichamelijke activiteit was 40%. De resterende actieve tijd werd voornamelijk besteed aan activiteiten met een lagere intensiteit dan lopen. Het energieverbruik tijdens lopen nam toe met de leeftijd en kwam tot uiting in een toename van de stapfrequentie en een afname van de regelmaat van voorwaartse en zijwaartse lichaamsversnelling tijdens lopen. Een jaar fitness training verminderde de leeftijdsgebonden toename van het energieverbruik tijdens lopen. Ouderen met een hoger lichamelijk activiteitsniveau en een betere conditie waren langer actief in de loop van de dag, terwijl proefpersonen met een lager activiteitsniveau meer sedentair werden in de middag. De leeftijdsgebonden toename van het energieverbruik tijdens de nacht was niet gerelateerd aan lichamelijke activiteit en een vermindering in slaap efficiëntie maar aan een afname van de kwaliteit van slaap.

Concluderend, bij ouderen is lopen een activiteit met een hogere intensiteit dan de overige activiteiten en levert zo een belangrijke bijdrage aan de dagelijkse lichaamsbeweging. Energieverbruik tijdens lopen neemt toe met de leeftijd en komt tot uiting in een verhoogde stapfrequentie en onregelmatige lichaamsversnelling in het horizontale vlak. Fitness training vertraagt de leeftijdsgebonden toename van het energieverbruik tijdens lopen. Fitte ouderen blijven langer actief gedurende de dag. De leeftijdsgebonden toename van het energieverbruik tijdens de nacht hangt niet samen met lichamelijke activiteit maar met een afname van de kwaliteit van slaap.

SOMMARIO

L'attività fisica rappresenta una funzione vitale fondamentale che diminuisce dopo il cinquantesimo anno di età. Un basso livello di attività fisica è associato ad una ridotta mobilità e ad un più alto rischio di mortalità negli anziani. L'attività fisica può essere misurata indossando un accelerometro, un piccolo dispositivo in grado di misurare le accelerazioni corporee e che può monitorare *pattern*, intensità e tipo di attività fisica. Il cammino è il tipo più comune di attività fisica ed il fabbisogno energetico di tale attività aumenta con l'età, il che potrebbe contribuire alla diminuzione dell'attività fisica.

Lo studio dell'attività fisica in soggetti anziani, con particolare attenzione al cammino e ai ritmi circadiani, può portare ad una maggiore conoscenza del declino dell'attività fisica associato all'età e suggerire possibili strategie d'intervento. In primo luogo, in questa tesi è stata estesa la validità di un accelerometro usato per monitorare l'attività fisica di soggetti in sovrappeso e obesi, in considerazione del fatto che il peso corporeo aumenta con l'età. In seguito, un accelerometro è stato utilizzato per descrivere l'importanza del cammino nel raggiungere livelli più elevati di attività fisica negli anziani e inoltre per individuare alcuni fattori che determinano il fabbisogno energetico del cammino. Successivamente è stato definito l'effetto di un programma di fitness per anziani sul loro fabbisogno energetico del cammino. Infine, è stato studiato l'effetto dell'invecchiamento sulla spesa energetica notturna durante le fasi del sonno e sui pattern di attività fisica.

I dati di trentasei soggetti sovrappeso od obesi sono stati analizzati al fine di generalizzare la validità di un accelerometro nel monitorare l'attività fisica. In seguito ventisei anziani non allenati, di età compresa tra i cinquanta e ottantatré anni, sono stati reclutati per seguire un programma di fitness della durata di un anno (gruppo training). I risultati del gruppo training sono stati confrontati con un gruppo di controllo di sedici soggetti, simile al gruppo training per età, peso, composizione corporea (calcolata da una misura del contenuto di acqua nel corpo), e livello di forma fisica (misurato come massimo consumo di ossigeno). Le misurazioni hanno avuto luogo prima e dopo l'anno di fitness. Il fabbisogno energetico quotidiano è stato misurato nel gruppo training per derivarne il livello di attività fisica. L'attività fisica è stata inoltre misurata come *activity counts* per mezzo di un accelerometro e monitorata per due settimane. Un algoritmo basato su template matching e sulla potenza del segnale è stato sviluppato per classificare gli *activity counts* come misurazioni prodotte durante attività di deambulazione e non. L'accelerometro è stato utilizzato anche per rilevare alcuni fattori determinanti del fabbisogno energetico del cammino misurato con tecniche di calorimetria indiretta su un *tapis roulant*. Infine, sono stati definiti alcuni fattori che influenzano il tasso metabolico notturno durante una notte spesa in una camera calorimetrica, misurando contemporaneamente le fasi del sonno con un polisonnogramma.

Gli *activity counts* in individui in sovrappeso od obesi sono stati in grado spiegare il 47% della varianza del livello di attività fisica, in linea con la validazione

condotta in soggetti magri. Negli anziani, gli *activity counts* derivanti da attività di deambulazione hanno rappresentato circa il 40% degli *activity counts* quotidiani e sono stati prodotti in circa il 20% del tempo speso in qualche attività. Il tempo speso in attività non deambulatorie è stato speso principalmente in attività di bassa intensità. L'aumento del fabbisogno energetico del cammino ha potuto essere in parte spiegato dall'aumento della frequenza del passo e dalla diminuzione della regolarità delle accelerazioni del corpo negli assi frontale e laterale. Un anno di fitness ha potuto ritardare l'aumento osservato nel fabbisogno energetico del cammino associato con l'avanzare dell'età. L'analisi dei pattern di attività fisica giornaliera ha rivelato che gli anziani con più alto livello di attività fisica e maggiore capacità aerobica sono stati in grado di rimanere attivi più a lungo durante il giorno, mentre i soggetti con livello di attività più basso sono risultati più inclini a rimanere sedentari nel pomeriggio. Durante la notte, l'aumento relativo del tasso metabolico associato con l'aumentare dell'età è stato influenzato da una diminuzione della qualità del sonno e non da una diminuzione dell'efficienza del sonno.

In conclusione, l'accelerometria è una tecnica valida per valutare l'attività fisica in individui in sovrappeso od obesi. Negli anziani, le attività di deambulazione costituiscono un importante contributo all'attività fisica e vengono intraprese ad intensità relativamente elevate. Il fabbisogno energetico del cammino aumenta con il progredire dell'età e questo aumento è associato con l'adozione di un passo più frequente e con un'accelerazione più irregolare del corpo sul piano orizzontale. Un anno di fitness ritarda l'aumento del fabbisogno energetico del cammino. Durante il giorno gli anziani più attivi sono in grado di mantenere livelli di attività più elevati più a lungo. Durante la notte l'aumento relativo del tasso metabolico rilevato all'avanzare dell'età è associato con una qualità del sonno inferiore, piuttosto che con una ridotta efficienza o con una maggiore attività notturna.

VALORISATION

Given that the western population is rapidly ageing, the impact of decreased physical activity on public health poses relevant challenges. Preventing chronic and debilitating diseases is the first aim of western countries health policies for older adults, and the promotion of physical activity is an important component of these policies. Accelerometers can provide valid assessments of physical activity, which is important for understanding relations between physical activity and health and for providing personalised feedbacks for lifestyle interventions. The validation of an accelerometer in overweight to obese described in this thesis provides scientific evidence that prediction equations validated in lean subjects can be used in populations with higher BMI. A valid prediction of physical activity level and activity energy expenditure can contribute to weight loss interventions, as physical activity can contribute to the maintenance of a lower body weight. However, the precision of this prediction is far from ideal and about half of the variance in physical activity level remains unexplained.

A phenomenon that limits the precision of assessments of physical activity is that different activities show different relationships between the associated energy expenditure and acceleration output. Classification models allow the recognition of activities and the consequent development of prediction equations that are activity-specific. Additionally, adopting such classifications can reveal the contribution of physical activity types. In this thesis, a classification algorithm was used to show that walking is a major contributor to physical activity in older adults. The prediction model developed after the classification was more precise than a simple linear equation based on unclassified accelerometry output. Thus, the application of classification systems in daily life improves physical activity assessments, allows detecting specific contribution of walking to physical activity level and offers the possibility to provide individuals with personalised motivational feedbacks in order to promote physical activity.

In addition to types of activity, motivational feedbacks can consider different time of the day. This thesis showed that sedentary older adults were more prone to sedentary activities in the afternoon. More active individuals maintained their activity level for longer and were more aerobically fit. Accelerometers, and in general wearable devices, are capable of detecting sedentary time and can be used to prompt individuals to be more active at day times when they tend to adopt more sedentary behaviours. A possible application of the results of this thesis is the implementation of a system of feedbacks. A wearable device can provide the feedbacks to prolong active morning bouts of physical activity thus promoting patterns showed by fitter and more active individuals.

Overnight, wearable devices can predict parameters of sleep, such as sleep efficiency. Such ability allows unobtrusive assessment of sleep behaviours in daily life. Applications of this ability include monitoring sleep patterns and their changes over time.

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CURRICULUM VITÆ

Giulio Valenti was born on 8 June 1987 in Trieste, Italy. After completing secondary school with focus on scientific subjects at the Liceo Scientifico Gandini in Lodi (Italy), in 2006 he started the study of Biomedical Engineering at the Politecnico di Milano. He obtained his bachelor's degree in 2009 after defending his thesis about signal processing of electroencephalographic signals in cognitive protocols. In 2011 he obtained his degree for the master Biomedical Engineering–Electronic Technologies and defended his master thesis in which he explored possible brain–computer interface applications of a commercial game controller based on biopotentials. His master included a one–year studying at the Universitat Polytechnica de Catalunya and the Universitat de Barcelona, thanks to the *Erasmus exchange programme*.

After the end of his master he moved to the Netherlands to start his four–year PhD project at the department of Human Biology of the Faculty of Health, Medicine and Life Sciences at Maastricht University under the supervision of Prof. dr Klaas Westerterp. The research performed during this period is described in this PhD–thesis entitled "Physical activity in older adults. Walking economy and circadian pattern". During his PhD trajectory Giulio presented several abstracts at national and international conferences. In February 2016 he starts as a research scientist at Philips Research in Eindhoven, working with the Ageing in Place group towards the extension of independent living in older adults.

LIST OF PUBLICATIONS

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Valenti G, Camps SG, Verhoef SP, Bonomi AG, Westerterp KR. Validating measures of free-living physical activity in overweight and obese subjects using an accelerometer. *Int J Obes (Lond)*. 2014 Jul;38(7):1011-4. doi: 10.1038/ijo.2013.195. Epub 2013 Oct 29.

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Awards

Young Investigator Awards: Best poster awards – granted for best poster at the conference *Recent Advances and Controversies in Measuring Energy Metabolism* (RACMEM). October 2014 in Tokyo, Japan.

Abbreviations

AEE activity energy expenditure.

BM body mass.

BMI body mass index.

BMR basal metabolic rate.

DLW doubly labelled water technique.

FFM fat-free mass.

ME mean error.

OMR overnight metabolic rate.

PA physical activity.

PAL physical activity level.

QS quality sleep.

REE resting energy expenditure.

REM rapid-eye movement.

SCN suprachiasmatic nucleus.

SD standard deviation.

SD_{cc} standard deviation of the cross-correlation function output.

SD_s standard deviation of the acceleration signal.

SE sleep efficiency.

SEE standard error of the estimate.

SMR sleeping metabolic rate.

SWS slow wave sleep.

TEE total energy expenditure.

TST total sleep time.

$\dot{V}O_{2\max}$ maximal oxygen uptake.

VAS visual analogue scale.

WASO wakeful moments in between periods of sleep.

WCost_{min} lowest energy needed to displace one kilogram of body mass for one meter while walking.

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