Development of prediction models to estimate activity-related energy expenditure under free-living conditions using accelerometry and its association with cardiometabolic factors

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List of abbreviations

Acc	accelerometer / accelerometry
ADP	air-displacement plethysmography
AEE	activity-related energy expenditure
AHA	American Heart Association
BIA	bioelectrical impedance analysis
BMI	body mass index
BMR	basal metabolic rate
CDC	Centers for Disease Control and Prevention
CN	condition number
CO_2	carbon dioxide (molecular)
COPD	chronic obstructive pulmonary disease
CPM	counts per minute
CRP	C-reactive protein
DIT	diet-induced thermogenesis
DLW	doubly-labeled water
EAT	exercise-related activity thermogenesis
EDTA	ethylene-diamine-tetra-acetate
FFM	fat-free mass
FM	fat mass
GLUT4	glucose transporter 4 (insulin-responsive)
HbA_{1c}	glycated hemoglobin
HDL	high density lipoprotein
HOMA	homeostasis model assessment (indicator for insulin resistance)
IC	indirect calorimetry
IDOM	database-assisted instrument for drug ascertainment (German: *Instrument zur datenbankgestützten Online-Erfassung von Medikamenten*)
IL	interleukin
IPAQ	International Physical Activity Questionnaire
IQR	interquartile range
LASSO	least absolute shrinkage and selection operator (variable selection technique)
LDL	low density lipoprotein
MET	metabolic equivalent of task
MVPA	moderate-to-vigorous physical activity
N	nitrogen
NEAT	non-exercise activity thermogenesis
NWT	non-wear time
O_2	oxygen (molecular)
PA	physical activity
QUAP	questionnaire of physical activity of previous 12 months
REE	resting energy expenditure
RMR	resting metabolic rate
RQ	respiratory quotient
SD	standard deviation

SE	standard error
SMR	sleeping metabolic rate
SOP	standard operating procedure
TEE	total energy expenditure
TNF	tumor necrosis factor
VIF	variance inflation factor
VM	vector magnitude
WHO	World Health Organization
95% CI	95% confidence interval

1 Introduction

The assessment of physical activity (PA) is of great concern in epidemiological and public health research, since the extent of PA plays an important role in the etiology of numerous chronic diseases and all-cause-mortality, and as modifiable lifestyle factor, PA is a favored target for disease prevention and health promotion [1-10]. However, less is known about the role of activity-related energy expenditure (AEE) and its relation to chronic diseases. According to the widespread definition of PA given by *Caspersen et al.*, AEE can be defined as the component of energy expenditure that is caused by 'any bodily movement produced by skeletal muscles' [11]. But the measurement of AEE under free-living conditions is a challenging task: AEE is derived as the remaining component of total energy expenditure (TEE) after basal or resting energy expenditure and diet-induced thermogenesis have been removed [12]. The standard reference method for measuring TEE under free-living conditions is the doubly-labeled water (DLW) method, while resting energy expenditure can be obtained by indirect calorimetry where the amount of oxygen consumption and carbon dioxide production is measured under fasting and resting conditions [13]. These time-consuming and cost-intensive methods are not feasible in large-scale epidemiological studies. Therefore, AEE has been traditionally derived from PA information that was collected via questionnaires and linked to metabolic equivalents (i.e. MET values) [14]. MET (metabolic equivalent of task) values quantify the average ratio of energy costs from specific activities or groups of activities in relation to the reference energy level of rested and quiet sitting [14-16], and can be used to classify PA intensity categories [17].

Since accelerometry technology has started to extend the field of PA measurement during the last decades, various devices are currently available to be used in epidemiological research. Accelerometers are small devices that are placed at specific sites of the human body and objectively record accelerations due to body movement in up to three planes; they can provide information about intensity, frequency and duration of PA [18].

Similar to the linking of PA information with MET values, the accelerometer output can be converted to (total) energy expenditure using device-specific algorithms. Commonly, these algorithms were developed under controlled laboratory conditions where standard activities were performed, such as treadmill walking in different speeds, with parallel measurement of energy expenditure via indirect calorimetry [19-22]. Additionally, individual factors such as sex, age, height, weight, or body mass index might be considered in the algorithm to finally estimate TEE or AEE [23-27]. However, the main drawback is that most of the underlying

algorithms are proprietary and not freely available. Consequently, it is unclear to what extent accelerometry-derived PA can explain the variance in AEE under free-living conditions, and to what extent additional individual characteristics could improve the estimation of energy expenditure.

In the frame of this thesis, these points were addressed by designing a study aiming at developing prediction models to estimate AEE based on accelerometry-derived PA parameters under free-living conditions. In this context, previous studies that examined the prediction of AEE based on accelerometry-derived PA information under free-living conditions were systematically reviewed and evaluated regarding to what extent accelerometer-derived PA and individual characteristics, as well as whether methodological study features (such as accelerometer device properties, study population characteristics) affect the variance in AEE explained by accelerometry-derived PA. Finally, based on the developed prediction models, the association of measured and predicted AEE as well as accelerometry-derived PA parameters with cardiometabolic factors, as indicators for chronic disease status, was investigated.

The following chapter gives background information on the components of energy expenditure, PA assessment methods in epidemiology with focus on accelerometry and a brief overview of current knowledge about the association of PA parameters and cardiometabolic factors as indicators or condition for chronic diseases.

2 Background

2.1 Total energy expenditure and its components

Total energy expenditure (TEE) consists of three main components: basal or resting energy expenditure (BEE, REE), diet-induced thermogenesis (DIT), and activity-related energy expenditure (AEE) (**Figure 2-1**) [13]. Beside their major determinants (which are described in the following paragraphs) these components can also be affected by internal and external factors such as emotion, stress, heat or cold, medication and diseases, resulting in changes in TEE (based on changes in at least one main component) or shifts in the proportion of main components relative to TEE [28].

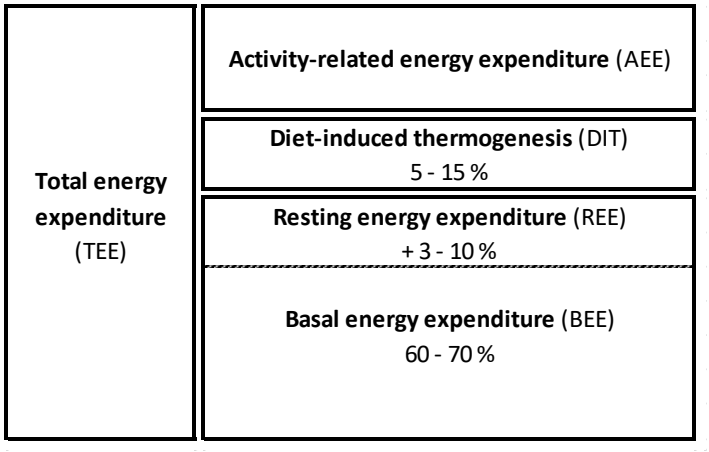

Figure 2-1 Components of total energy expenditure

The reference method for TEE measurement under free-living conditions is the doubly-labeled water (DLW) method. This noninvasive technique was developed by *Lifson et al.* [29, 30], and was first applied in humans by *Schoeller and Santen* [31]. DLW contains stable isotopes of hydrogen (^{2}H, deuterium) and oxygen (^{18}O). After oral administration, the isotopes distribute evenly within the body water and then exit the body continuously as water (both isotopes ^{2}H and ^{18}O) and carbon dioxide (only ^{18}O isotopes). Samples of body water sources (urine, blood, saliva) are collected at the beginning, (optional) during, and at the end of the measurement period, and the contained amount of ^{2}H and ^{18}O isotopes is measured via isotope-ratio mass spectrometry [32]. The difference in the elimination rates of ^{2}H and ^{18}O isotopes is an estimate of the CO_2 production rate, which is subsequently used to calculate TEE [29-31].

Assumptions concerning isotope fractionation (in water vapor, in breath water, non-sweat water loss), dilution space of isotopes in the body, change of body water volume over measurement period (estimated by body weight), background isotope levels, and an estimate of the respiratory quotient, which is based on the macronutrient composition of the diet,

should be considered in the calculation [29-35]. Further, to reduce analytical errors and improve accuracy and precision of TEE measurement, the following factors should be taken into account: (1) use of individually weighed DLW dose (e.g. dependent on body weight) to get an optimized isotope enrichment in the body [32, 36]; (2) choice of length of measurement period (7 – 14 days, optimal length is about two biological half-lives of isotopes) [32, 36]; (3) procedures of sample collection, processing and storage (using standardized protocols) [32]; (4) choice of an experienced laboratory for isotope measurement [32, 36, 37]; (5) take samples in duplicate or triplicate to reduce measurement error [32].

Validation of TEE measured by DLW against TEE measured by indirect calorimetry (24 hours respiration chamber stay) or controlled food intake yielded mean differences and standard deviations ranging between -2 % and 6 % and between 1 % and 8 %, respectively [35]. The within-subject variation for TEE measured by DLW is 8 % [38].

The main advantages of the DLW method are that it is suitable for all populations [18, 39, 40], induces no changes in physical activity behavior [39], and provides accurate and valid estimation of TEE in free-living conditions [18, 39, 40]; the main limitations are its high costs [18, 39], the need of experienced laboratory and analysis facility [39], and missing opportunity to provide detailed information on EE components or physical activity intensity, frequency or duration [18, 39-42].

2.1.1 **Basal energy expenditure**

Basal energy expenditure (BEE; synonym: basal metabolic rate, BMR) represents the energy that is needed to maintain all essential vital functions of the body. As the major component of daily energy expenditure, BEE corresponds on average to 60 – 70 % of TEE [13]; whereas in very active individuals the proportion is lower [43]. Determinants of BEE are sex, age, body composition, height and also genetic and hormonal factors [42], with fat-free mass as the primary determinant [44, 45].

The difference between BEE and resting energy expenditure (REE; synonym: resting metabolic rate, RMR) emerges from measurement conditions [46], although in literature the distinction is not consistent and terms are even used equivalently [28].

The most common principle to determine BEE or REE is indirect calorimetry: the amount of oxygen consumption and carbon dioxide production is measured and then converted into energy expenditure using established formulas [47-50]. Several measurement approaches of indirect calorimetry are available, of which ventilated open-circuit systems, such as ventilated canopy or respiration chamber, are mostly established [46].

To achieve comparable measurements, standardized protocols should be considered. For BEE measurement via indirect calorimetry, complete rest before and during measurement, fully awake state, supine position, 10 – 12 hours fasted state, thermoneutral environment and no emotional stress are demanded conditions [51]. The measurement should be conducted in the morning, optimally after awaking from sleep [46].

As these conditions would require an overnight stay at the measurement location, which is often not feasible for practical reasons, REE could be measured instead, where the condition regarding measurement directly after sleep is neglected [46]. Consequently, due to slight locomotion activity prior to the measurement, conditioned by getting out of bed and reaching the measurement location, or other methodological variations (e.g. sitting position), REE can be 3 – 10 % higher than BEE [13, 46].

Alternatively to the complex measurement via indirect calorimetry, BEE and REE can be estimated from established prediction formulas that have been developed in several populations considering differences in sex, age or body mass index [52-55].

2.1.2 **Diet-induced thermogenesis**

Diet-induced thermogenesis (DIT; synonym: thermal effect of food, TEF) represents the energy that is needed for digestion of consumed food, which includes absorption, processing and storage of nutrients. DIT is mainly determined by energy content and macronutrient composition of food, especially the protein proportion [56, 57]. Under conditions of healthy state, energy balance and mixed diet consumption, DIT corresponds on average to 10 % of TEE [57, 58]. For the single nutrients, the thermic effect related to energy content is 5 – 10 % for carbohydrates, 0 – 3 % for fat, 20 – 30 % for proteins, and approximately 20 % for ethanol [58, 59].

The measurement of 24-hour DIT is very complex and not feasible under free-living conditions due to practical reasons. When AEE or other components of energy expenditure need to be determined, DIT is often assumed as 10 % of TEE [57, 58], or it is disregarded because of its small and therefore negligible amount [43]. Another alternative is to measure DIT of a test meal and extrapolate the value to 24-hour energy intake [43]. However, this approach does not consider the individual variability in the macronutrient composition over the whole day(s) and therefore might be misleading.

Under laboratory conditions, daily DIT is standardly assessed by measuring energy expenditure over (at least) 24 hours in a respiration chamber using indirect calorimetry. When the subjects'

BEE, REE or sleeping energy expenditure is determined as reference energy expenditure level, standardized meals according to individual energy requirements are served to measure postprandial energy expenditure continuously over 24 hours, which subsequently has to be corrected for spontaneous activity (detected by radar sensors or accelerometer) using different approaches [60-66]. The difference between the corrected 'activity-free' postprandial energy expenditure and the reference energy expenditure level reveals 24-hour DIT, which is expressed in absolute numbers or as percentage of energy intake.

DIT consists of an obligatory component, which can be calculated following certain assumptions of substrate pathways [48, 49, 58], and a facultative or adaptive component, which modulates the degree of nutrients' energetic utilization to regulate an over- or undersupply of energy intake to maintain energy balance [67], but also to ensure the supply with essential nutrients in conditions of unbalanced diets with low protein content or low-quality proteins [67-69]. Probably relevant mechanisms for adaptive DIT are the regulation of futile cycles in the metabolization or transport of substrates, protein turnover, and sympathetic nervous system-mediated mitochondrial uncoupling in skeletal muscle, brown or white adipose tissue [67, 69-73].

Although DIT contributes the smallest part to TEE, it has high biological within-subject variability (15 – 40 % relative error) even under optimal measurement conditions [74, 75]. The variability can be attributed to (unknown) adaptive regulations due to physical activity (especially exercise) or diet composition of previous day(s) [74-77], body mass index or obesity [67, 78], or genetic and hormonal factors [78, 79]. Additional determining factors of DIT emerge from eating behavior or eating patterns, such as meal frequency and meal size [56, 62], timing of meals [62, 80], food consistency [81], palatability [62, 77], and fast-or-slow eating [56, 82]. Thus, when DIT is estimated, it has to be considered that all determinants are potential sources of errors that would sum up in measured DIT, and that cannot be captured in a standardized measurement setting.

2.1.3 **Activity-related energy expenditure**

Activity-related energy expenditure (AEE; synonym: activity-induced thermogenesis) represents the energy that is expended by skeletal muscles during any kind of bodily movement [11]. AEE is the most variable component of TEE; in sedentary individuals with very low activity levels AEE averages 15 % of TEE, whereas in highly active individuals AEE averages to at least 50 % of TEE [83-85]. Depending on the intention of the performed activity, AEE can

be divided into exercise-related activity thermogenesis (EAT), which includes energy expenditure resulting solely from exercise and sports activities, and non-exercise activity thermogenesis (NEAT), which is the major part of AEE and includes energy expenditure resulting from all other activities and postures during daily routine [85].

Two common approaches to estimate AEE in free-living settings are (1) to calculate the difference of TEE and its other components REE or BEE and DIT; and (2) to use a factorial approach, where types of activities and their duration are captured and assigned to energy equivalent values [85]. Both approaches show potential sources of errors: Calculating AEE from measured TEE, BEE, REE and DIT involves methodologically complex techniques, as described in the preceding paragraphs; thus, measurement errors of each single component would accumulate in the final AEE estimate [67, 86]. Regarding the factorial approach, potential sources of errors arise from the ability and accuracy of the used instruments to capture human activities (e.g. questionnaires, logs, activity monitors), and from the validity of their assumed energy costs [85].

Methodological applied, a valid estimate of AEE can be used for validation of new measurement methods of physical activity (such as questionnaires, activity monitors, accelerometers) by associating AEE derived from doubly-labeled water-based measurements with AEE derived from physical activity measurement techniques [87-90]. Content-related, AEE plays an important role in the regulation and control of body weight because of its high intra- and inter-individual variability [60], and is therefore of great interest in the field of obesity research [85], and all related chronic diseases, such as metabolic syndrome or cardiovascular diseases [91-93].

The close relationship between physical activity (as a behavior) and AEE (as a consequence of this behavior) [11, 94], provides the basis for the concept of the factorial approach and for the prediction of AEE in free-living settings. The challenge is to capture the entirety of activities involved in human movement to give an accurate measure of physical activity, and to assign an accurate (individual) energy equivalent, which might depend on individual characteristics such as age, sex, height, body composition, health status, or hormone status.

New technologies of objective activity monitoring might enable an improved detection of physical activity as the primary determinant of AEE, and consequently, the opportunity to investigate the potential of additional parameters in affecting AEE.

2.2 Physical activity in epidemiology and public health

2.2.1 Concepts and characteristics of physical activity

The widespread definition of *Caspersen et al*. defines physical activity as 'any bodily movement produced by skeletal muscles that results in energy expenditure' [11].
A more conceptual definition given by *Pettee Gabriel et al.* defines physical activity as a 'complex and multidimensional […] behavior that involves human movement, resulting in physiological attributes including increased energy expenditure and improved physical fitness' [94]. Both definitions underline the mutual relation between physical activity—as the behavioral and active part—and energy expenditure and physical fitness—as the consequential part that is associated with health-related outcomes [94].

The close interrelationship between physical fitness and physical activity and their relation to health has been proposed in several concepts [94-96], defining physical fitness as a set of attributes that people have or achieve that allows performing physical activities in daily life [11, 97]. These attributes of physical fitness were commonly assigned to health-related components (cardiorespiratory endurance, muscular endurance, muscular strength, body composition, flexibility) or skill-related components (agility, balance, coordination, speed, power, reaction time) [11, 97]; and they mediate the effect of physical activity on energy expenditure. Nevertheless, an essential distinction between physical fitness and physical activity is the intra-individual day-to-day variability, which is low for physical fitness, but high for physical activity [18].

Based on the concept of *Pettee Gabriel et al.*, physical activity, as a multidimensional behavior, is influenced by physiological, psychological, social and environmental factors that should be considered for an appropriate measurement of physical activity [94]. Further, sedentary behavior is related to physical activity as well, but represents an independent component of the behavioral profile [94].

Physical activity can be characterized qualitatively, quantitatively and contextually.
Qualitative characteristics include the *type* of physical activity (such as walking, cycling, tennis), and the *domain* that refers to the environmental setting in which physical activity takes place; the four commonly defined activity domains are (1) household, domestic, self-care; (2) occupation; (3) transport, locomotion; and (4) leisure time [18, 94]. The term exercise or sports refers to only one element of physical activity belonging to the leisure time domain, and

is defined as planned, structured and repetitive activities aiming at improving or maintaining physical fitness; thus exercise and physical activity are not synonymous [11, 94].

Contextual characteristics include attributes regarding time and place, position or posture of performed activities [98].

Quantitative characteristics include the three dimensions *frequency, duration* and *intensity.*

The *frequency* refers to the number of times a specific activity or activities of a certain intensity were performed within a predetermined time period; *duration* refers to the amount of time that was spent on these activities; and *intensity* refers to the level of effort that is reached while performing the activity [94]. Based on frequency, duration and intensity the calculation of (activity-related) energy expenditure can be provided [18], which can be regarded as a processed quantitative measure of physical activity. Moreover, all activity monitoring devices are calibrated and validated against energy expenditure measured by indirect calorimetry (in laboratory settings) or doubly-labeled water (in free-living settings) [98].

To identify intensity levels of specific activity types, the widespread Compendium of Physical Activities provides activity-specific MET values, which describe the rate of energy expenditure in relation to quite sitting and can be used to calculate individual energy costs of self-reported activities [14, 16-18]. Nevertheless, the relative intensity of a performed activity remains a subjective evaluation and can depend on age, physical fitness, and bout duration [99].

2.2.2 **Measurement methods of physical activity in epidemiology**

The complex and multidimensional nature of physical activity makes the measurement of human movement quite challenging [41, 94]. Although there are various methods to measure physical activity in human populations, it is impossible to measure all characteristics of physical activity with one single method [18]. Traditionally, questionnaires have been used to measure 'reported' physical activity [100], and recently accelerometers entered the field that allow an objective assessment of physical activity based on the detection of acceleration due to body movement [18]. However, all methods have limitations, so finally the research question and study design will determine the most suitable method or combination of methods [98]. Several reviews and reports gave an overview on the strengths and limitations of the available measurement methods of physical activity, which are summarized in **Table 2-1** (subjective methods) and **Table 2-2** (objective methods).

Table 2-1 Subjective methods to measure physical activity

Subjective methods	Strengths	Limitations
Questionnaires (self-reported, interviewer-assisted) **Recalls**	• appropriate for general population [18, 41, 42] and specific target groups [41] • appropriate for large-scale studies [40, 42, 101] • low costs [18, 40, 41, 101, 102] • low respondent burden, easy applicable [18, 41, 102, 103] • versatile tool, can be adapted to suit the population of interest [42, 103] and to answer specific research questions [41] • can provide information on classification of PA status [42, 101-103], frequency, duration and intensity of performed activities, PA domains, PA types, PA patterns, dose-response-relationships depending on complexity [18, 40-42, 101-103] • PA and EE estimation more valid on group level [18, 42, 102] • surveillance tool [18]	• limited validity and reliability (at individual level) [102, 104, 105] • less valid in young children and elderly, proxy reporters are required [18, 42, 105] • not appropriate to quantify EE at individual level [104] • recall bias [18, 40, 101-103], reporting bias [103], social desirability bias [18, 102], information bias [41], risk of misclassification due to misinterpretation of questions [41, 102] • difficulties of respondents to average frequencies and duration of PA during the past week(s) or month(s) or year(s) [18, 103] • overestimation of vigorous PA [42] • underestimation of daily living activities [42] • under- and overestimation of PA can be influenced by social desirability, age, complexity of questionnaire, seasonal variation, length of period surveyed [102]
Records, Diaries, Logs	• low costs [41] • accounts for PA in short time intervals, e.g. each 15-minute period [42] • provide detailed information on PA types, PA pattern, intensity level, duration, domains, body positions [41, 42, 103]	• high participant burden [41, 42, 103] • risk of incompleteness [40, 41] • may influence PA behavior [41, 42] • time-consuming encoding of entries [41]
Observation	• no respondent burden [18] • provide detailed quantitative and qualitative information on PA (frequency, duration, intensity, type) for specific time frame [18, 40, 102]	• high costs for personnel, trained observer needed [18, 40] • time-consuming [41, 102], labor-intensive [18] • subjectivity of observer [102] • observer presence may artificially alter PA pattern [18], potential reactivity [102] • monitoring of a limited time frame [18, 102] • not convenient for large-scale studies [102]

Abbreviations for Table 2-1 and Table 2-2: AEE activity-related energy expenditure, EE energy expenditure, GPS global positioning system, HR heart rate, MVPA moderate-to-vigorous physical activity, O_2 oxygen consumption, PA physical activity.

Table 2-2 Objective methods to measure physical activity

Objective methods	Strengths	Limitations
Pedometry	• assessment of most common activities: walking, running [18, 42, 101] • suitable for all populations [18, 40] • suitable in free-living conditions [102] • low respondent burden, easy to use (portable, lightweight, noninvasive, nonreactive) [18, 40, 42, 101, 102] • relatively low costs [18, 40, 42, 101, 103] • relatively easy data collection and analysis [18] • register movements in vertical direction to derive number of steps [42, 102] • provide accurate and reliable information on steps count (especially at higher walking speeds) [40, 42, 102, 103, 106], (less accurate) on walking distances and EE [40, 102, 106], on total amount of daily movement [102] • motivational tool, behavioral feedback due to easily understood metric [42, 101, 103]	• inability to detect non-ambulatory activities [18, 40, 101-103] and postures [103] • not appropriate for people with large proportion of activities without vertical movement [102] • no information about intensity, frequency, duration of movement [18, 102] or type of PA [40] • less accurate and reliable assessment of steps count at slow walking speeds [40, 42] • less accurate for EE estimation (during free-living) [18, 101, 102, 106], and distance assessment (at slower and higher speeds) [42, 101, 106] • proprietary algorithms to determine steps [103] • variation of output depending on wear position [42] • potential Hawthorne effect [18]
Accelerometry	• suitable for laboratory and free-living conditions [101, 102] • suitable for all populations across all age groups [18, 40] • suitable for monitoring over weeks in real time [18, 42, 103] • low respondent burden, easy to use (noninvasive, small size) [18, 40, 42, 101, 103] • relatively easy data collection [18] • improved software packages simplify data analysis [18] • register movements in up to three planes [102] • extensively validated tool [40] • can provide information on frequency, duration, intensity of PA [18, 40, 42, 103], overall PA [42, 102], time spent in activities of varying intensities [18], PA patterns [40] • accurate estimation for locomotion activities [18] • linear relationship between counts and EE [18, 102] • valid for free-living AEE estimation on group level [18]	• inability to detect static activities [42] with isometric muscle contraction [41], carrying loads [18, 40, 41], incline walking [18, 40, 41, 102], upper body movements (when placed at hip, waist) [18, 40, 102], water activities (when not waterproof) [40], cycling [18, 40, 102], non-ambulatory activities [98] • lack of sensitivity on sedentary and light-intensity activities [98, 103] • body placement can influence measurement [40] • no information about type of PA [40] • complex and time-consuming analysis [40, 103] • proprietary methods to process acceleration signals, arbitrary "count" value [18, 98, 107] • financial costs may prohibit assessment of large numbers of participants [18, 40] • external vibration can lead to artefacts [108-110] • validity for EE estimation is limited [102] and varies between monitors and types of activity [18, 101] • underestimation of EE in incline walking [18, 40, 102], carry loads [18, 40, 41], static activities [41, 42] • low precision of (regression based) AEE estimation on individual level [18] • varying thresholds for PA intensity categories can lead to misclassification [18] and difficulties in between-study-comparisons [42] • potential Hawthorne effect [41, 42]

For explanation of abbreviations see *Table 2-1*

Table 2-2 *Continued*

Objective methods	Strengths	Limitations
Heart rate monitoring	• direct measurement of a physiological parameter (related to PA) [18, 42, 103] • relatively low costs [18, 40, 42, 101, 102] • applicable in controlled settings and free-living conditions [42, 101] • suitable for majority of populations [18, 40] • low respondent burden for short periods (noninvasive, versatile, unobtrusive, waterproof) [18, 40, 101, 102] • easy and quick data collection [18, 40] • can provide information on frequency, intensity, duration of (high-intensity) PA [18, 40, 42, 102] • valid EE estimation for high-intensity activities on group level and dynamic activities [18], based on linear relationship between heart rate (HR) and oxygen (O_2) consumption [41, 42, 102, 103]	• indirect measure of PA (related to physiological response of PA) [102] • initial (individual) calibration of HR-PA relationship (Flex-HR-Point) needed [40, 102] • HR-O_2 (EE) relation differs between upper and lower body activities [42], and varies between and within individuals [18] • only useful for high-intensity or aerobic activities [18, 40], inaccurate for detecting sedentary and very low-intensity activities [42, 101, 102] • unreliable EE estimation in low-intensity PA [18, 40, 42], in rest [42], and extremely high-intensity PA [40] • HR can be affected by conditions unrelated to PA, like body temperature, food intake (caffeine), gender, genetics, body posture, metabolism, medication, age, time of day, fitness level, (emotional) stress, smoking [18, 40-42, 101, 102] • potential discomfort of wearing over long periods of time [103], poor compliance [41] • potential Hawthorne effect [41] • electrical or magnetic interference from common electrical devices [101]
Combined sensors (Accelerometry + Heart rate)	• combines strengths of accelerometer and HR monitors (see above) • determination of non-wear-times with HR [18] • improved EE estimation by accelerometer at low-intensity levels and by HR at high-intensity levels (branched equation modeling) [18, 42] • more valid and precise EE estimation (at group level) [18, 42, 102], especially for non-ambulatory activities [103]	• relatively high costs [18, 103] • complex data processing and analysis [18, 40] • initial (individual) calibration of monitors needed [18] • potential inconvenience and discomfort of wearing [103] • subject's competence for correct placement of devices [18]
Global Positioning System (GPS)	• provide real-time information on distance, speed, altitude, location [40, 103] to derive information about frequency, duration, intensity and spatial context of PA [40, 111] • complement to accelerometry [112, 113] • often incorporated in new technology devices (e.g. fitness tracker, smartphone) [42, 114]	• relatively high costs [40] • complex data processing and analysis [40, 112] • limited to outdoor activities (with higher speed movement) due to required satellite connection [40, 111, 112] • risk of data loss due to limited battery capacity and signal dropouts [111-113]
Fitness tracker (e.g. Fitbit ®, Jawbone® , Nike©)	• low respondent burden, high acceptability in wearing (lightweight, unobtrusive, waterproof) [115, 116] • include various measurement functions (pedometer, accelerometer, GPS, altimeter, heart rate, temperature) [103, 116] • provide information on steps count (valid), walking distance (inaccurate) [40], EE or calories, sleep, active minutes [103, 116] • high inter-device reliability for step counts, sleep, and EE [116] • self-monitoring and motivational tool, behavioral feedback [116, 117] • useful for intervention purposes [116]	• accuracy not well known [103], inconsistent validity criterion measure [116] • underestimation of EE [40, 42, 117], and step counts at slower walking speeds [116, 117] • over- and underestimation for distance at slower or higher speeds [116, 117] • overestimation of MVPA, and sleep time [116, 117] • potential reactivity, change in activity behavior [116] • proprietary algorithms, data output controlled by companies [116, 117] • no data access [116] • non-wear times not considered in outputs [116]

For explanation of abbreviations see *Table 2-1*

2.2.3 **Accelerometry**

As the focus of this thesis lays on accelerometry as measurement method for physical activity, more technical information on measurement principle and functionalities of accelerometers is given in this chapter.

Technically, accelerometers are sensors that determine acceleration along a sensitive axis [109]. Although there are different types of sensors (e.g. piezoelectric, piezoresistive, capacitive), of which the advanced ones can detect both dynamic acceleration (due to body movement) and static acceleration (due to gravity), basically all sensors operate on the same principle ('spring mass system'): acceleration leads to movement of the (seismic/silicon) mass that causes a displacement of the integrated movable plate or spring; this disproportion produces an electrical voltage signal that is proportional to the applied acceleration [108, 109, 118]. This analog signal is filtered, (often) amplified, and sampled at a predetermined frequency to be converted in a digital signal and stored as a raw acceleration signal in g-units [108]. Further signal processing by applying analytical algorithms result in the common accelerometer output 'activity counts' [108]. Thus, an 'activity count' can be defined as a dimensionless accelerometer output that originates from processed and converted acceleration signals.

All internal processing steps (filtering, amplifying, sampling, converting, signal integration) affect the accelerometer output and can differ between accelerometer devices from different manufacturers, between consecutive accelerometer generations of the same manufacturer, and even within the same device that was used with different firmware versions, so that the accelerometer outputs—activity counts or raw acceleration—are not directly comparable [108, 119-121].

To ensure inter- and intra-device reliability for accelerometer outputs and reduce variability between devices, calibration procedures (optimally prior to every use) or post-measurement adjustments are recommended, not only for each directly measured output (e.g. acceleration, body posture, heart rate) but also for derived outputs (e.g. intensity-specific thresholds, energy expenditure) [122-125].

Likewise, external features can influence the measurement and output that have to be considered when applying accelerometry; several guidelines have been published giving advice on how to select the appropriate recording period, placement at the body, epoch length, data transformation and analysis, decision on valid days, treatment of non-wear time, and outcome of interest [126-128].

The ongoing progress in technical development enables improved signal detection, storage capacity, battery life, data processing, and fusion of multiple sensor outputs, which can improve measurement of physical activity characteristics [119, 129]. Thus, the list of available activity monitors with accelerometer sensors is still growing [119].

2.2.4 Physical activity dose-response relationship and association with cardiometabolic factors

It is well known that physical activity (PA) has beneficial effects on health by reducing the risk of many chronic diseases, such as cardiovascular diseases, type 2 diabetes, cancer, and all-cause mortality [4-10]. To achieve these benefits, the World Health Organization (WHO) [130] and other international guidelines [3, 131, 132] recommend to spend at least 150 minutes per week in PA with moderate intensity, or 75 minutes in PA with vigorous intensity, or an equivalent combination.

This recommendation suggests that each PA intensity would have the same beneficial effect, as long as PA is performed in its respective duration; consequently, this implies that only the volume of PA (= intensity * accumulated duration) counts. Furthermore, worldwide 31 % of the adult population (43 % America, 48 % United States, 35 % Europe) fails to meet these recommendations [133-135], which further initiates the discussion whether lower intensity levels of PA could also have beneficial effects on health [136, 137].

Commonly, MET values are assigned to PA intensities categories to quantify the average energy costs in relation to basic energy level (= 1 MET) that corresponds to rested and quiet sitting [14-16]. According to this classification, sedentary behavior corresponds to < 1.5 METs, light PA to 1.5 – 2.9 METs, moderate PA to 3.0 – 5.9 METs, and vigorous PA to $\geq$ 6.0 METs [3, 138]. Depending on PA measurement method, these MET cutoffs are assigned to device-specific outputs (e.g. accelerometer counts) or to specific activity types derived from questionnaires [14]. For example, using the triaxial accelerometer Actigraph GT3X (ActiGraph LLC., Pensacola, FL, USA) *Sasaki et al.* defined 2690 – 6166 vector magnitude counts per minute (VM cpm) as moderate intensity PA, 6167 – 9642 VM cpm as vigorous intensity PA, and $\geq$ 9643 VM cpm as very vigorous intensity PA [139]; accordingly, $\leq$ 2698 VM cpm would be defined as light intensity, which would also include sedentary behavior in this example. With additional information of duration and frequency of performed activities, the total PA volume can be calculated (e.g. in MET-hours per week).

Many studies described a curvilinear dose-response relationship between PA volume (= intensity * accumulated duration) and disease or mortality risk [4, 6, 7, 140, 141], however shapes and slopes might vary between different health outcomes due to diverse physiologic pathways [140]. The highest risk occurs at levels of inactivity, but with increasing PA volume, the risk is decreasing with a declining trend, having the greatest potential for risk reduction at lower PA volumes [4, 140], whereas at very high PA volumes the potential for additional risk reduction might be rather small [6, 140]. Thus, there is no lower limit for beneficial effects [4, 99, 140], and - so far - no clear upper limit for adverse effects [4, 6, 7, 140, 142]; although, in some studies with women and cardiac patients, subjects at the highest examined activity level had an increased mortality or disease risk compared to lower activity levels [143-146]. Some studies also postulate an 'optimal dose' of PA volume (of leisure time), where risk reduction is maximal and additional increase in PA volume would not lead to additional significant risk reduction [6, 7, 141]. This 'optimal dose' of PA volume corresponds to about 3 to 5 times the recommended minimum of PA [6, 141].

While the effect of frequency and duration of activity bouts might be similarly covered by total PA volume, the effect of PA intensity might be not, because performing vigorous intensity activities, such as running or jogging, requires different physiologic conditions compared to low intensity activities, such as walking [140]; thus for some health outcomes the intensity of PA might play a more essential role beyond its contribution to total PA volume.

Many studies examined the relation between specific PA intensity levels and its association to chronic diseases or cardiometabolic marker as indicators for chronic disease status or processes [147]. Traditionally, most studies concentrated only on moderate and vigorous intensity PA, as these categories were easy to capture via questionnaires that focused on sports, exercise or other leisure-time activities. But since accelerometers and other activity monitor devices are available, light intensity PA is of growing interest, because this fraction represents the major part of daily living activities and was not considered in the guidelines so far [74, 136, 137, 140]. So this would allow to cover all domains of PA. Given that many people do not meet the recommendations [133-135], the discussion about which dose of PA is necessary to achieve health benefits is ongoing. Further complexity is added since the potential health benefits of the distinct PA intensities might depend on age, current health status or comorbidities [6, 7, 141].

So far many cross-sectional, longitudinal/prospective and interventional studies described favorable associations in adults between PA of light intensity [136, 137, 148-153], moderate intensity [152], vigorous intensity [152, 154-156], or moderate-to-vigorous intensity [149, 151, 153, 157-161] and cardiometabolic factors of the lipid metabolism [136, 137, 151, 152, 154, 158-160], glucose metabolism [136, 137, 150, 152, 153, 155-160], or inflammation [137, 149, 151-153, 158, 160-162], which were considered within the scope of this thesis. Some of these studies focused on special populations, such as individuals with type 2 diabetes [150] or women with gestational diabetes [161], pregnant [151] or postmenopausal [153] women.
However, to interpret and evaluate the results adequately, methodological issues regarding PA measurement have to be considered, such as PA measurement method, thresholds for intensity levels, definition of non-wear time and valid days, duration of wear time, adjustment for complementary intensity categories or total PA volume or sedentary behavior, respectively; or number and characteristics of study participants.

2.3 Public health relevance

Physical activity (PA), as modifiable lifestyle factor, is a favored target for disease prevention and health promotion [138]. Numerous investigations have shown that (more) active individuals have a lower risk for chronic diseases such as cardiovascular diseases, diabetes, several types of cancer, and all-cause mortality [4-10]. Also in respect of disease treatment, physically active patients can improve prognosis and health outcomes of diabetes [163, 164], different types of cancer [165-168], or COPD/respiratory diseases [169, 170].

Since medical costs have been growing continuously over the last years [171, 172],—in part caused by demographical changes with a growing proportion of aging people who are at higher risk for multiple comorbidities, or by an increase of chronic diseases due to adverse lifestyle habits, such as unhealthy diet, inactivity or sedentary behavior—intervention strategies promoting PA seem promising to lower costs and improve health status effectively [173-175].

Available data often rely on subjective and self-reported PA resulting in dichotomous classification of being ‘inactive’ or ‘active’ with respect to the commonly accepted WHO recommendations [130]. New available technologies, such as accelerometry, allow an objective and more accurate quantitative assessment of (overall) PA, which can improve detecting differences and changes in PA over time within and between individuals, comparing different (groups of) populations, or validating and evaluating intervention programs [41].

Further, an accurate PA assessment is essential to quantify the dose-response relationships between PA and health outcomes and to identify their causal associations, and to finally establish public health recommendations [41, 103].

With this new input of technology-based PA assessment, the widespread recommendations on PA (spending 150 – 300 minutes of moderate PA or 75 – 150 minutes of vigorous PA or an equivalent combination) [130] might be updated by including also light intensity PA [136-138], and by promoting an increase in total PA volume, independent of PA intensity or length of activity bouts [138]. The identification of low-intensity PA is particularly important for sedentary and elderly people, not only for quantifying total PA and estimating AEE [176], but also because there is no minimum threshold at which PA starts to be effective for positive health outcomes [99].

Similarly, the objective technology-based PA assessment might also improve the quantification, characterization and prediction of AEE to further investigate associations between AEE and potential disease outcomes, biomarkers or genetic variations in large-scale epidemiologic studies.
In the German National Cohort, a large-scale, population-based, multicenter, prospective cohort study, currently accelerometer devices are used to assess PA [177], but no measurement of energy expenditure is performed. Developed prediction models based on accelerometer-derived PA measures would allow an estimation of AEE in this study population for subsequent analyses, such as investigating the association of AEE and chronic disease risks.

Moreover, AEE is a major target for regulating and controlling body weight [85], because it varies strongly between and within individuals [60]. An accurate characterization and estimation of AEE might support strategies for preventing and treating overweight and obesity, as well as related comorbidities, such as type 2 diabetes, several types of cancers, cardiovascular diseases or metabolic syndrome [91, 93, 178-180].

3 Objectives

This thesis focused on the development of a prediction model to estimate activity-related energy expenditure (AEE) based on accelerometry-derived physical activity data, where both energy expenditure and physical activity measurements were conducted under free-living conditions.

Today many accelerometers from various manufacturers are available and most of them have implemented algorithms to provide AEE estimates. But most of these algorithms are proprietary without access to details of considered parameters, and they were developed under controlled conditions based on a limited number of predefined activities.

In the first part of this thesis, a systematic review was conducted to summarize studies that examined the prediction of AEE based on accelerometer-derived physical activity parameters under free-living conditions, to further investigate (1) to what extent the variance in AEE was explained by accelerometer-derived physical activity output, (2) to what extent methodological conditions (such as study design, accelerometer device properties, characteristics of the study population) influence the explained variance in AEE, and (3) to what extent additional parameters (such as age, sex, body composition) can improve the prediction of AEE.

In the second part of this thesis, considering the results of the systematic review, a study in German adult volunteers was designed (ActivE study) aimed to develop prediction models estimating DLW-derived AEE based on accelerometry-derived physical activity and additional factors, and further to investigate (1) determinants of AEE, (2) appropriate accelerometer output variables for AEE prediction, and (3) appropriate additional variables beyond accelerometry to predict AEE. During the model development process, different variable settings were considered creating alternative models for different available variable sets, to enable a broad utilization, for example in the German National Cohort study that used the same accelerometer device and similar examination methods.

In the third part of this thesis, based on the developed prediction models, the association of measured and predicted AEE, as overall physical activity parameter, with cardiometabolic factors of the lipid metabolism, glucose metabolism and inflammation, as indicators for chronic disease status or processes, was investigated using the data of the ActivE study in a secondary analysis. Regarding the WHO recommendations on physical activity to spend at least 150 minutes per week in physical activity with moderate intensity, or 75 minutes per

week in physical activity with vigorous intensity, or an equivalent combination [130], which suggests that each intensity level has the same beneficial effect given the respective duration of physical activity—this hypothesis should be examined. Thus, the association between intensity and duration of physical activity with cardiometabolic factors was investigated considering three intensity categories of accelerometer-derived physical activity (low, moderate, vigorous), but also time spent in total activity regardless of intensity level.

4 Methods

4.1 Systematic review on prediction of activity-related energy expenditure based on accelerometer-derived physical activity under free-living conditions

4.1.1 Search and selection of publications[1]

This systematic review was conducted searching MEDLINE database (online National Library of Medicine® journal citation database) via PubMed. The following text terms were used: energy expenditure AND (prediction OR estimation OR validation OR regression OR model) AND (accelerometry OR accelerometer OR motion sensor OR activity monitor) AND (activity OR exercise). Preliminary search output was additionally filtered for humans (species), adult 19+ years (ages), English, German (languages), and full text (text availability) using the preset PubMed filter options. Publication date was only restricted at the end to 31 December 2014[2].

First, title and abstract of articles were screened to assess eligibility. In a second step, and in case the abstract screening was inconclusive, the full text article was screened. Articles were excluded if they failed to (1) examine AEE, (2) use accelerometers to measure physical activity, (3) examine populations of adults aged 18 years or older, (4) set up the study under free-living conditions by using the DLW method, and (5) report original research data. Further, the references cited in the included articles but also references of reviews or meta-analyses of similar scope were screened to identify additional articles considering the eligibility criteria.

During the article selection process it turned out that included articles could be differentiated into two groups: (1) articles, that examined the association between DLW-derived AEE and accelerometry-derived physical activity data, and in some cases particularly to predict DLW-derived AEE using accelerometry-derived physical activity data, and (2) articles, that focused on validation of the accelerometers by comparing the AEE obtained from DLW method with AEE generated automatically by the accelerometers (based on proprietary and mostly not available algorithms). This systematic review focused only on articles that belong to the first group, all articles of the second group were excluded.

[1] In the framework of this thesis, parts of the method on "Search and selection of publications" have already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

[2] In the context of this thesis, an updated literature search was conducted on January 5th 2017 using the publication date 'to 31 December 2016' in the filter options. No additional articles were found to be included in this review (Appendix Figure 10-4).

4.1.2 **Data extraction**[3]

Information from included articles was extracted according to the following categories and items:

- First author and year of publication
- Characteristics of study population: type of population, sample size, sex, age (range or mean), body mass index or alternatively weight (range or mean)
- Accelerometer-specific features: device name, type of accelerometer, body position, overall period of data recording, daily wear time, accelerometer output metric
- Energy expenditure specific features: duration of DLW measurement, measurement or calculation of resting/basal/sleeping metabolic rate, consideration of diet-induced thermogenesis, AEE calculation
- Results of association and prediction (if reported): crude R^2, total R^2, partial R^2
- Analysis approach of prediction model, predictors of final model(s), not included factors

Crude R^2 was defined as the variance in AEE explained solely by accelerometer output with no other predictors included in the model. Total R^2 was defined as the variance in AEE explained by accelerometer output and additional predictors, and partial R^2 as the variance in AEE explained by accelerometer output when other predictors are included in the model. If R^2 was not directly reported, it was calculated from reported correlation coefficients R.

With regard to the subsequent analysis the following determinations were defined. Articles that reported on using more than one accelerometer device [90, 181-183] or examining several subpopulations [39], each device and population group was treated as a separate study in the analysis. In those studies that reported more than one prediction model [39, 184-188], only the model that explained the largest variance (total R^2) along with the lowest number of included predictors (most parsimonious model) was considered in the analysis. In those studies that included interaction terms in the prediction model [39] or conducted stratified analyses (e.g. by sex) [189], both the interaction term and the stratification variable were treated as additional predictors in the analysis. In those studies that did not report the mean age of the study population, it was substituted by averaging the minimum and maximum age of the study population [39, 182, 190]. In those studies that reported more than one accelerometer output metric from the same device, only the more advanced output metric *counts per day* [90, 183, 187] or *vector magnitude counts per day* [183, 188] was considered for the analysis. Moreover,

[3] In the framework of this thesis, parts of the method on "Data extraction" have already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

accelerometer output metrics referring to *time spent per intensity category* were not considered in the analysis either [184, 191-193]. In those studies that examined not only absolute AEE but additionally AEE relative to body weight (AEE per kg), [39, 90, 185, 194, 195] only the results according to absolute AEE were considered in the analysis. However, a sensitivity analysis was conducted with regard to this issue (more details in the following paragraph).

4.1.3 **Statistical analysis of systematic review**[4]

To examine whether the association between accelerometer output metric and DLW-derived AEE was affected by characteristics of the study population or certain accelerometer features, the relation of explained variance in AEE (crude R^2, total R^2) and study characteristics was analyzed in a meta-regression approach using nonparametric tests. Continuous characteristics (sample size, mean age) were assessed using Spearman rank correlation and illustrated as scatter plots. Categorical characteristics (accelerometer's body position, recording period, wear time, type of accelerometer output, accelerometer output metric) were assessed using Mann-Whitney U-test or Kruskal-Wallis test and illustrated as boxplots. In those studies that improved the explained variance in AEE by including additional predictors beyond the accelerometer output metric, the improvement from crude R^2 to total R^2 was assessed with Wilcoxon signed rank sum test and illustrated as boxplots. Further, the relation of total R^2 and improvement of R^2 with number of additional predictors beyond accelerometer output metric was analyzed using Kruskal-Wallis test.

Sensitivity analyses were conducted to evaluate whether considering AEE as absolute measure or relative to body weight (AEE per kg) would affect the association between AEE and accelerometer output metric (crude R^2), and also the relation of crude explained variance in AEE and the study characteristics. For this purpose, first, crude R^2 was compared between all those studies that reported AEE as absolute measure and all those studies that reported AEE relative to body weight using Mann-Whitney U-test (between-group comparison). Studies that reported both measure variants were considered in both groups. Second, focusing only on this particular group of studies that reported values for both absolute and relative AEE [39, 90, 185, 194, 195], crude R^2 was compared using Wilcoxon signed rank sum test (within-group comparison).

[4] In the framework of this thesis, parts of the method on "Statistical analysis of systematic review" have already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

The statistical software SAS Enterprise Guide, version 4.3 (SAS Institute Inc., Cary, NC, USA) was used for analyses, and boxplots and scatter plots were generated using Microsoft Excel 2010 (Microsoft Corporation). Two-tailed p-values <0.05 were considered as statistically significant.

4.2 ActivE study

4.2.1 Study design

The ActivE study was designed as cross-sectional study. The primary aim was to develop a prediction equation for AEE based on accelerometry-assessed physical activity data and additional factors. Further, in a secondary analysis the association of duration and intensity of physical activity with factors of inflammation and of the lipid and glucose metabolism was investigated.

Based on the primary study aim, the sample size was calculated defining an alpha-level of 0.05, a power of 0.8 and a partial correlation of 0.4 or 0.57 between accelerometer output variable and AEE as found in reference studies with similar study design [185, 188]. Depending on the number of predictors in the model the calculated sample size amounted to 22 or 47 participants if two predictors were included, and to 24 or 49 participants if four predictors were included (Appendix **Table 10-1**). Consequently, a sample size of 50 participants was determined that should complete the study protocol successfully.

Individuals were included if the following criteria were met: age 20 – 69 years, body mass index (BMI) 18.5 – 35.0 kg/m², German language skills, being under daily life conditions, and ability to give informed consent. Individuals were excluded if one of the following criteria was met: inability to complete the study protocol successfully, pregnancy or lactation period (a pregnancy test was performed in premenopausal women beforehand), addiction to drugs or alcohol, claustrophobia, cardiac pacemaker, cardiovascular disease (specifically angina pectoris, heart insufficiency, aortic stenosis), diabetes type 1 or type 2, instable thyroid disease, food allergy or intolerance to foods of the test meal, great weight changes during the last six months (>10 kg), participation in weight reduction programs during the last three months, hemophilia, or intake of medication interfering with energy expenditure (specifically intake of beta-blockers or centrally acting anti-hypertensives, intake of more than three medications for high blood pressure treatment). In case eligible individuals had acute infections, participated in other studies or were on vacation during the proposed time of examination, the participation in the ActivE study was postponed.

To allow for more variability, both sexes were equally considered and a broad range of age and BMI was predefined for sample recruitment. The recruitment scheme was designed as shown in **Figure 4-1**; 50 participants (25 men and 25 women) should have been recruited. For each sex and each 10-years age category (20 – 29 to 60 – 69 years) five individuals were selected out of which two individuals were normal weight (BMI 18.5 – 24.9 kg/m²), two individuals were overweight (BMI 25.0 – 29.9 kg/m²) and one individual was obese (BMI ≥ 30.0 kg/m²).

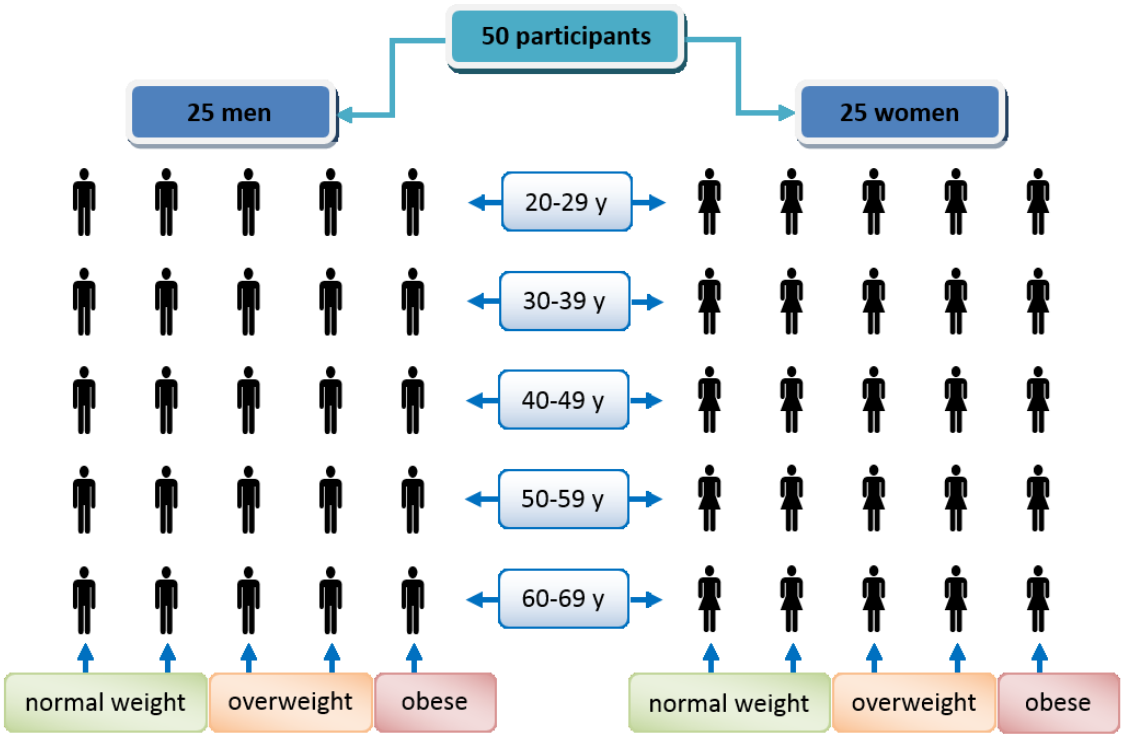

Figure 4-1 Recruitment scheme of target sampling

Participants were recruited via institutional mailing lists of Max Delbrück Center for Molecular Medicine in the Helmholtz Association (MDC) and Charité - Universitätsmedizin Berlin, Campus Berlin Buch, as well as announcements in local daily, weekly or monthly newspapers (“Berliner Zeitung”, “Märkische Oderzeitung”, “Bucher Bote”), and flyers that were distributed at local events (“Lange Nacht der Wissenschaften 2013”) and local drug stores.

4.2.2 Ethics and Data protection

The study protocol was approved by the responsible ethics committee of the Charité - Universitätsmedizin Berlin and the local data protection officer. All participants gave written informed consent prior to study entry.

4.2.3 Study protocol and definition of variables

4.2.3.1 Timeline of examinations for each participant

The examination of participants took place from September 2012 until April 2014. Each participant visited the study center at the beginning (day 1) and at the end (day 15) of the 2-week examination period (**Figure 4-2**). At the first visit, after giving informed consent, measurements of anthropometry, body composition, blood pressure, handgrip strength, a personal questionnaire-based interview including drug intake of previous seven days, and a standardized activity program while wearing an accelerometer were conducted. Further, blood samples were taken and the basal urine sample for DLW analyses was collected. During the next two weeks, the participants were instructed to wear the accelerometer continuously and to document non-wear times in a provided diary, as well as time of going to bed and getting up each day, and (optional) leisure activities. Further, the participants were instructed to collect five DLW urine samples at defined time points and to keep a dietary record for at least seven days. At the second study center visit, anthropometry and body composition were measured repeatedly, the last DLW urine sample was collected, resting and postprandial energy expenditure was measured in a respiration chamber, and each participant completed a questionnaire about physical activity of the previous 12 months (QUAP).

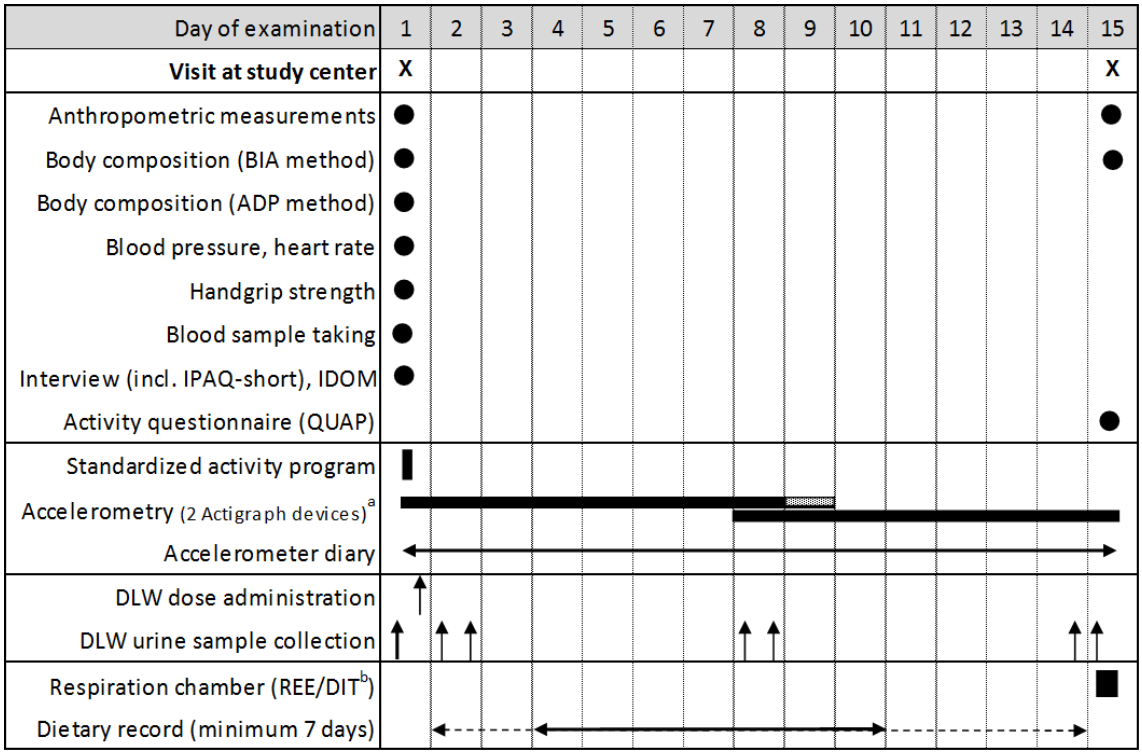

Figure 4-2 Examination schedule for participants of ActivE study.
[a] The overlap of recording periods of the two accelerometers was originally on day 8 and was extended to days 8 and 9 during the study (detailed description in paragraph 4.2.3.14). [b] DIT of served test meal. ADP air-displacement plethysmography, BIA bioelectrical impedance analysis, DIT diet-induced thermogenesis, DLW doubly-labeled water, IDOM database-assisted instrument for drug ascertainment, IPAQ international physical activity questionnaire, QUAP questionnaire of physical activity of previous 12 months, REE resting energy expenditure.

4.2.3.2 Total energy expenditure measured by doubly-labeled water method

The average daily total energy expenditure (TEE) was determined using the doubly-labeled water (DLW) method over a 2-week period according to an adapted version of the Maastricht protocol (SOPnr. M0105, Vers.01, date: 13.02.2002) [33]. Deviating from the standard protocol, but in agreement with our project partners from University of Maastricht (Faculty of Health, Medicine and Life Sciences; Department of Human Biology & Movement Sciences), the basal urine sample was collected at the midmorning during the first study center visit.

On day 1 before going to bed, each participant consumed an individually weighed DLW dose, based on each participant's previously self-reported body weight. After overnight equilibration of DLW isotopes the first enriched urine sample was collected from the second voiding on the next morning (day 2). During the next two weeks participants were instructed to collect further urine samples: on day 2 from a voiding in the evening, on day 9 from the second voiding in the morning and from a voiding in the evening, on day 14 from a voiding in the evening, and on day 15 from the second voiding in the morning. In almost all cases the last urine sample was collected during the morning of the second study center visit. Date and time of each collected urine sample was documented.

In Maastricht the concentration of DLW isotopes in each of the six urine sample was measured in duplicate using an isotope-ratio mass spectrometer. The results of average daily TEE in *MJ/day* were provided and converted in *kcal/day* as follows:

$$TEE\ [kcal/day] = TEE\ [MJ/day] * 1000 / 4.1868 \quad \text{(Eq. 1)}$$

Five potential participants cancelled the participation in the study before the examination started. For already ordered and individually weighed DLW doses surrogate participants of same sex and similar body weight were sought. The selection of each surrogate participant was coordinated with the partners in Maastricht to make sure that the DLW doses matched appropriately.

4.2.3.3 Physical activity measured by accelerometry

Daily physical activity was determined over the 2-week examination period using the triaxial accelerometer ActiGraph GT3X+ (ActiGraph LLC., Pensacola, FL, USA), that was placed at the right hip with an elastic belt. The proprietary software ActiLife (ActiGraph LLC., Pensacola, FL, USA) was used to initialize the accelerometers (software version 6.4.X to 6.7.3), to download the data, and to determine activity parameters (software version 6.11.9). Four different generations of GT3X+ devices were used in the study (NEO1E, NEO1F, CLE1A, CLE1B) with

automatically updated firmware (for CLE-devices: 1.1.22 to 2.2.1, for NEO-devices: 2.5.0 to 3.2.1).

Accelerometers were initialized to record raw data at 100 Hertz sample rate using all three spatial axes. The *Idle sleep mode* was disabled to avoid an automatically reduced sample rate in periods without movement (for example during sleeping or quiet sitting). Individual information of participants (sex, date of birth, measured height, measured body weight, race, dominance ['dominant' for right-handed, 'non-dominant' for left-handed individuals]), start time and stop time of recording period, and predefined configurations for placement of accelerometer (limb = 'waist', body side = 'right') were entered during the initialization process.

Due to limited storage capacity and battery life of the accelerometer under the specified conditions, data recording would be possible for a maximum of ca. 10 days. Therefore, each participant was equipped with a second pre-initialized accelerometer device starting data recording automatically after one week. Thus, the whole 2-week examination period was covered with at least 1-day-overlap (**Figure 4-2**). The first device recorded data from day 1 to the end of day 8 (23.59 h), and the second device recorded data from the beginning of day 8 (00.00 h) to the end of the second study center visit on day 15.

The participants were instructed to wear the accelerometer continuously 24 hours per day, except for water activities, sauna visits, or activities with high body contact and to switch to the second accelerometer device on day 8 (because this day is recorded on both devices). The time of accelerometer change as well as non-wear times and their reasons should be documented in a provided diary. In addition, the participants were asked to document the time of going to bed and getting up each day. The documentation of time of leisure activities or sports was optional in order not to burden the participants further.

Along with the download, the raw signals were automatically converted into counts. An epoch length of one second was used to condense the data. Automatically derived parameters of interest were average *counts per minute* (cpm) of each of the three single axes (y, x, z) and of the combined vector sum of the three axes, called vector magnitude (VM), as well as average *steps per day* and *steps per minute*.

The data sets of the two accelerometers were merged at the time point of changing devices, which was determined from scatterplots of the 1-second *VM cpm* signals, while extreme signals due to taking the first device off and putting the second device on were minimized. After excluding the incompletely recorded days 1 and 15, a total of 13 consecutive days per participant were available for further calculations, which are described in detail in paragraph

4.3.1. Prior to these calculations, a non-wear time analysis was performed using ActiLife. Based on current findings for 24-hour accelerometry in free-living conditions [196], two hours of consecutive zeros in *VM cpm* without permission for any interruptions were defined as non-wear time.

4.2.3.4 Anthropometric measurements including body composition

Anthropometric measurements included body height, body weight, waist circumference, hip circumference and body composition and were performed at the first and second study center visit. Participants were overnight-fasted, emptied bladder previously, and wore light and close-fitting clothes or underwear. Shoes, socks, jewelry and other accessories were removed. Additionally, for body composition examination, participants were asked to avoid exercise 3 – 4 hours prior to the measurement.

Body height was measured with a stadiometer (SECA 240, Hamburg, Germany) to the nearest 0.1 centimeter. Body weight was measured with an electronical, digital scale (part of seca mBCA 515, Hamburg, Germany) to the nearest 0.05 kg. Circumferences of waist and hip were measured with a flexible, non-elastic measuring tape (seca 201, Hamburg, Germany) to the nearest 0.1 centimeter according to recommended measurement protocols of the WHO [197]. Body mass index (BMI) and waist-to-hip ratio (WHR) were calculated as:

$$BMI\ [kg/m^2] = body\ weight\ [kg] / (body\ height\ [m])^2 \quad \text{(Eq. 2)}$$

$$WHR = waist\ circumference\ [cm] / hip\ circumference\ [cm] \quad \text{(Eq. 3)}$$

According to WHO guidelines [198] BMI was classified as normal weight (18.5 – 24.9 kg/m²), overweight (25.0 – 29.9 kg/m²) or obese (≥ 30 kg/m²).

Body composition was determined using two different measurement techniques: bioelectrical impedance analysis (BIA) and air-displacement plethysmography (ADP).

The principle of BIA is based on electrical impedance measurement of the human body and is used to estimate the content of total body water and body cell mass [199]. In this study, BIA was performed using the medical Body Composition Analyzer (seca mBCA 515, seca gmbh & co. kg., Hamburg, Germany) that enables segmental impedance measurement using four pairs of electrodes [199]. The participants stood in a standardized position, so that the balls and heels of the feet and the fingers of both hands (with a finger separator between middle and ring finger) have contact to a total of eight electrodes. Impedance was measured with a

current of 100 µA and implemented frequencies ranging from 1 – 1000 kHz, with 50 kHz as default for parameter output. By means of the proprietary software (seca analytics mBCA 115, seca gmbh & co. kg., Hamburg, Germany) the parameters were saved automatically after each measurement and exported at the end of the study period. The following parameters were used for analysis:

- *Absolute fat-free mass in kilogram (FFM_{BIA})*
- *Absolute fat mass in kilogram (FM_{BIA})*
- *Relative fat mass in percent ($FM\%_{BIA}$)*
- *Relative fat-free mass in percent ($FFM\%_{BIA}$)*

Since the BIA measurement was performed twofold and on both study center visits, there were usually four parameter sets for each participant. For analysis, chronologically the first available parameters were used.

The principle of ADP is based on the invers relation of pressure and volume under isothermal conditions (Boyle's Law) in a hermetic closed chamber and is applied in whole body densitometry [200]. In this study ADP was performed using the BodPod system (BOD POD®, PN #2102946, Life Measurement, Inc., Concord, CA, USA). After a two-point chamber calibration using a calibration cylinder of defined volume, the body volume of each participant was determined due to change in pressure with and without the participant inside the BodPod chamber. Participants wore close-fitting clothes or underwear, a bathing cap to compress the hair, and were sitting upright in a standardized position [201]. Two measurements of body volume were conducted and averaged. If the two measurements differed more than 150 ml a third measurement was performed and the closest two measurements were averaged [201, 202]. The measured body volume was automatically corrected by the proprietary software for surface area artefact and predicted average thoracic gas volume [201]. By means of initially measured body weight with an integrated and calibrated scale connected to the BodPod system, the software calculated body density, and finally percentage of body fat using Siri's equation [203]. For analysis, the following parameters were used:

- *Absolute fat-free mass in kilogram (FFM_{ADP})*
- *Relative fat-free mass in percent ($FFM\%_{ADP}$)*
- *Absolute fat mass in kilogram (FM_{ADP})*
- *Relative fat mass in percent ($FM\%_{ADP}$)*

4.2.3.5 Blood pressure

Systolic and diastolic blood pressure and heart rate were measured threefold after initial 5-minute rest in sitting position and with 2-minute breaks between each measurement at the right arm using a fully automatic hemodynamometer (HEM 705 IT, OMRON, Healthcare Europe B.V. Mannheim, Germany). Cuff size was selected as specified by the manufacturer (normal size cuff for arm circumference <32 cm; big size cuff for arm circumference ≥32 cm), after measuring the right upper arm circumference [197]. All three measurements were performed in a standardized position: sitting straight and relaxed, knees bent with an angle of 90 degrees, the right lower arm lying on table with palm upturned. Participants were instructed not to speak during and between the measurements. The arithmetic mean of the second and third measurement was calculated to derive the following parameters that were used for analysis:

- *Systolic blood pressure in mmHg*
- *Diastolic blood pressure in mmHg*
- *Resting heart rate in beats per minute*

4.2.3.6 Handgrip strength

The isometric handgrip strength was measured to the nearest 0.1 kg using Jamar Plus digital dynamometer (Patterson Medical, Sammon Preston, Bolingbrook, IL, USA). According to previous investigations and recommendations of the American Society of Hand Therapists dynamometer's grip width was adjusted at position 2 [204, 205]. Measurements were performed in a standardized position: sitting upright with feet on the ground, shoulders adducted and neutral rotated, elbow bent in 90° angle and wrist in neutral position [205]. By command participants started to press the grip with maximum power without exhaling on exertion. Starting with the right hand, each side was measured threefold alternately. The maximum value out of six measurements was used as parameter in analysis:

- *(Maximum) handgrip strength in kilogram (HGS_{max})*

4.2.3.7 Blood sample taking and measured parameters

Blood samples were taken in the morning of the first study center visit. Participants were overnight-fasted (11.4 – 15.4 hours after last meal), and were instructed to drink only water or sugar-free tea at this morning. According to standard operating procedures, blood was taken from cubital vein without applying any compression. Samples of serum, EDTA-plasma and buffy coat were obtained. Within six hours after blood sample taking, serum and EDTA-plasma aliquots were delivered to an external clinical laboratory (hospital Laborverbund Brandenburg-

Berlin, site Bernau; and their partner laboratories) and blood parameters were analyzed according to standard procedures. For analysis, the following parameters were used:

- *Total cholesterol in mmol/l*
- *HDL-cholesterol in mmol/l*
- *LDL-cholesterol - measured and calculated - in mmol/l*
- *Triglycerides in mmol/l*
- *Cholesterol-HDL-ratio*
- *C-reactive protein in mg/l (CRP)*
- *Glucose in mmol/l*
- *Glycosylated hemoglobin in % (HbA_{1c})*
- *Insulin in mU/l*
- *C-peptide in ng/ml*

Additionally, HOMA index (Homeostasis Model Assessment) was calculated as [206]:

$$HOMA\ index = insulin\ [mU/l] * glucose\ [mmol/l] / 22.5 \quad \text{(Eq. 4)}$$

Due to restructuring in the external laboratory during the study period C-peptide was measured at two different laboratories providing different units of values (ng/ml and nmol/l). For analysis, all values were converted in ng/ml by multiplying nmol/l values with factor 3.02 according to the homepage of one laboratory site [207].

4.2.3.8 Resting energy expenditure measured by indirect calorimetry

Resting energy expenditure (REE) and postprandial energy expenditure were estimated by measuring carbon dioxide (CO_2) production and oxygen (O_2) consumption applying the indirect calorimetry method in a respiration chamber.

The respiration chamber (2.5 m x 2.0 m, 2.2 m height) is an airtight room that is constantly supplied with fresh air (open-circuit system). The chamber is equipped with a comfortable armchair, table, television/DVD, radio/CD, toilet, intercommunication system, an air-conditioning for keeping the room temperature at a comfortable and thermoneutral level and generating a constant air flow towards the measuring sensors, two cameras for monitoring the subject, three passive infrared sensors for recording the movement of the subject, and an air lock for passing test meals to the subject or samples from the subject to the investigator during the measurement phase without interrupting the air flow measurement. The concentration of O_2 and CO_2 is measured continuously in the input air and in the output air by

two sensors (CO_2 with infrared sensors, O_2 with paramagnetic sensors). Further, air flow, air temperature, humidity and air pressure are measured continuously in the output air.
For calculation of the final CO_2 production rate and O_2 consumption rate, the air volume was adjusted to standard conditions (temperature = 0 °C, pressure = 760 torr, humidity = 0 %) [208], and the most recent gauging and calibration factors were applied. Finally, measurements were summed up and exported as values per 10-minute intervals by the corresponding software. An overview of the construction, technical data and calculation basis of the respiration chamber is attached in the appendix (Appendix **Figure 10-2**).

The standardized examination in the respiration chamber was performed at the second study center visit (day 15). Participants were instructed to refrain from doing exercise and drinking alcohol the day before, and to have the last meal, which should be low in proteins, until 21.00 h. The overnight-fasted participants entered the chamber in the morning of the second study center visit.
After a 30-minute adaptation phase for air equilibration, the CO_2 and O_2 measurements started. The first 40 minutes of CO_2 and O_2 measurement were used to calculate the REE and the resting respiratory quotient. The participants were instructed to sit as quiet and relaxed as possible during this phase. After completed REE measurement, a standardized test meal was served and should be eaten within the next 10 minutes. The following postprandial phase lasted 240 minutes. For this study, only the REE measurement was considered.

<u>Calculation of nitrogen excretion rate (in resting phase)</u>

For REE calculation O_2 consumption and CO_2 production was taken into account, as well as nitrogen excretion. Nitrogen excretion rate was estimated by measuring the concentration of the nitrogen-containing compounds urea, ammonia/ammonium, creatinine, and uric acid in two urine samples that were collected before and after REE measurement. From the concentration of the nitrogen-containing compounds, the excreted nitrogen (N) of each compound was calculated and summed up (Eq. 5). Of each urine sample, the mass of the whole voiding and the specific weight were measured to calculate the urine volume (Eq. 6). Considering the times of urine sample collection (Eq. 8) and the amount of excreted nitrogen per urine sample (Eq. 7), the nitrogen excretion rate [mg/min] for the resting phase was calculated (Eq. 9).

Sum of excreted N [mg/ml] from urea, ammonium, creatinine, uric acid	=	*(Urea [mol/l] * 28.0134 g N/mol) + (Ammonium [mol/l] * 14.0067 g N/mol) + (Creatinine [mol/l] * 42.0201 g N/mol) + (Uric acid [mol/l] * 56.0268 g N/mol)*	(Eq. 5)

Urine volume of whole voiding [ml]	=	$\frac{\text{Urine mass of whole voiding [g]}}{\text{Specific weight of urine sample [g/ml]}}$	(Eq. 6)

Amount of excreted N [mg] of REE urine sample	=	*Sum of excreted N [mg/ml] * Urine volume [ml]*	(Eq. 7)

Time interval [min] for resting phase	=	*Time of voiding before REE measurement – Time of preceding voiding (at home)*	(Eq. 8)

N excretion rate [mg/min] for resting phase	=	$\frac{\text{Amount of excreted N [mg]}}{\text{Time interval for resting phase [min]}}$	(Eq. 9)

Calculation of energy expenditure, REE and RQ

Based on established formulas [209, 210], energy expenditure for each 10-minute interval was calculated as:

$$EE_i = 16.18 * O_2\ rate_i + 5.02\ CO_2\ rate_i - 5.99\ N\ rate_i\ /\ 1000 \quad \text{(Eq. 10)}$$

where *EE = energy expenditure of the i-th interval [kJ/min]*

O_2 rate = oxygen consumption rate of the i-th interval [ml/min]

CO_2 rate = carbon dioxide production rate of the i-th interval [ml/min]

N rate = nitrogen excretion rate of the i-th interval [mg/min]

REE was calculated as mean of EE rates of the intervals 1 to 4, which correspond to the first 40 minutes of CO_2 and O_2 measurement, and the individual nitrogen excretion rate in the resting phase. For better understanding REE was converted in *kcal/day* as:

$$REE\ [kcal/day] = REE\ [kJ/min] * 60\ [min] * 24\ [hours] / 4.1868 \quad \text{(Eq. 11)}$$

The respiratory quotient (RQ) for each 10-minute interval was calculated as:

$$RQ_i = CO_2\ rate_i\ /\ O_2\ rate_i \quad \text{(Eq. 12)}$$

Similarly, the fasting RQ of the resting phase was calculated as mean of RQs of the intervals 1 to 4, which correspond to the first 40 minutes of CO_2 and O_2 measurement.

4.2.3.9 Personal interview

Information about sociodemographic factors (age, sex, school education, professional training/qualification, occupation), lifestyle factors (smoking, frequency of alcohol consumption, physical activity of last seven days [IPAQ-Short], sleep duration) and medical history was collected in a personal questionnaire-based interview.

Participant's *age* was calculated in years using information of birth month and year, which was collected during the interview, and the date of the first study center visit. For descriptive overview and checkup of the recruitment schedule, 10-year *age groups* were generated (20 – 29, 30 – 39, 40 – 49, 50 – 59, 60 – 69 years).

Information about *school education* ("Schulabschluss") was determined by a multiple-choice question with 10 options to answer that were summarized for the analysis as follows:
(1) *Qualification for university/college entrance* (comprised "Fachhochschulreife", "Abitur/Hochschulreife", "Abitur über 2. Bildungsweg")
(2) *No qualification for university/college entrance* (comprised "Realschulabschluss", "Abschluss Polytechnische Oberschule 10. Klasse")
One participant, who stated to have another graduation ("anderer Schulabschluss"), was assigned to one of the above mentioned categories based on his additional free text explanation. There were no participants in the categories "Hauptschulabschluss", "Abschluss Polytechnische Oberschule 8./9. Klasse", "Schüler/in", or "ohne Abschluss".

Information about *professional training qualifications* ("Ausbildungs-/Berufsabschluss") was determined by a multiple-choice question with multiple answers that were assigned into two categories as follows:
(1) *Completed vocational/educational training* (comprised any vocational or educational training, master school or vocational academy graduation)

(2) *Completed academical training* (comprised any college or university graduation [i.e. bachelor's, master's, diploma's or magister's degree, or completed state examination or doctorate])

If professional training was not yet completed, participants were asked about the target qualification, and this answer was treated as the completed trainings for the analysis. Three participants used the option *"*einen anderen beruflichen Abschluss" and additionally explained their qualification in their own words as free text. These answers were assigned to one of the above mentioned categories. There were no participants without any professional qualification.

For analysis, this information was categorized as follows:

(A1) *Completed vocational/educational training*

(A2) *Completed academical training*

(A3) *Completed both vocational/education and academical training*

Additionally, another modified 2-category-variable was generated, which represented only the highest completed qualification.

(B1) *Completed vocational/educational training as highest qualification*

(B2) *Completed academical training as highest qualification*

Information about *occupation* ("Erwerbstätigkeit") was determined by a multiple-choice question with 11 options to answer that were summarized for the analysis as follows:

(1) *Full-time employed* ("Vollzeit erwerbstätig")

(2) *Part-time employed* (comprised "Teilzeit erwerbstätig", "Altersteilzeit", "geringfügig erwerbstätig/400 Euro/Minijob", "unregelmäßig, gelegentlich beschäftigt")

(3) *Not employed* ("nicht erwerbstätig [Schüler, Studenten, Arbeitslose, Rentner, Vorruheständler ohne Nebenverdienst]")

There were no participants in the categories "Ein-Euro-Job bei ALGII", "In beruflicher Ausbildung/Lehre", "Umschulung", "Bundesfreiwilligendienst, FSJ, FÖJ", or "Beurlaubung".

The *medical history* was determined considering the following diseases and medical findings: myocardial infarction, angina pectoris or disease of the coronary blood vessels, cardiac insufficiency or heart failure, stroke/apoplexy, cardiac arrhythmia, hypertension, diabetes mellitus, increased triglycerides and/or cholesterol level, thyroid disease, and cancer. In case of pre-existing conditions, additional information about first appearance, type and duration of treatment in general and during the last 12 months was collected.

Information about *smoking status* was determined by a multiple-choice question with the following 3 options to answer:

(1) *Never smoker*

(2) *Current smoker*

(3) *Former smoker*

Subsequently, current and former smokers were asked how long and how many cigarettes, and cigars, cigarillos or pipes they used to smoke or had smoked, respectively. For analysis, *pack years of smoking* were calculated (Eq. 13) assuming that one pack consists of 20 cigarettes, and that one pipe corresponds to two cigarette equivalents [211]. Never smokers were considered with 'zero' pack years in the calculation.

$$\textit{Pack years of smoking} = \frac{\textit{Number of smoked cigarettes/equivalents per day}}{\textit{20 * Years of smoking}} \qquad \text{(Eq. 13)}$$

Information about *frequency of alcohol consumption* was determined by a multiple-choice question with 5 options to answer that were summarized for analysis as follows:

(1) *1x per week or less* (comprised "1x pro Monat oder weniger", "2-4x pro Monat")

(2) *More than 1x per week* (comprised "2-3x pro Woche", "4x pro Woche oder mehr")

There were no participants in the category "Niemals".

Information about *physical activity* (PA) was determined by the adapted short version of the International Physical Activity Questionnaire (**IPAQ-Short**) [212]. This validated questionnaire collects information about time spent in activity of vigorous and moderate intensity, time spent in walking and time spent in sitting (on week days) during the last seven days [213]. Participants were asked to consider all activities in all domains (leisure time, occupation, transport, domestic- and garden work) that lasted for at least 10 minutes.

By indicating, firstly, the number of days with activity during the last seven days, and secondly, the average duration (minutes or hours) per active day, subsequently the daily *average duration (minutes per day)* was calculated for each activity category (vigorous / moderate / walking / sitting). An additional question was asked to determine the average *sleep duration* (including napping) in *hours/day* ("Wie viele Stunden schlafen oder ruhen Sie durchschnittlich pro Tag insgesamt?").

The following set of parameters was derived and used for analysis:

- *Time in vigorous PA [minutes/day]*

- *Time in moderate PA [minutes/day]*
- *Time in walking activity [minutes/day]*
- *Time spent sitting [hours/day]*
- *Time spent sleeping (including napping) [hours/day]*

Further, additional parameters were calculated by adding up several activity categories:

- *Total time in moderate PA and walking activity [minutes/day]*
- *Total time in moderate and vigorous PA [minutes/day]*
- *Total time in moderate and vigorous PA and walking activity [minutes/day]*

4.2.3.10 Questionnaire of physical activity of previous 12 months (QUAP)

Information about physical activity in the previous 12 months was determined using a questionnaire that was developed by a research team of the German Cancer Research Center (DKFZ, Heidelberg, Germany). The questionnaire considered the activity domains *occupation* ("Erwerbstätigkeit"), *domestic work and gardening* ("Arbeiten im/am Haus, in der Wohnung oder im Garten"), *locomotion by foot and bicycle* ("Fortbewegung"), *leisure time activity spent with walking and bicycling* ("Freizeitaktivität"), *sports and exercise* ("Sport und Bewegung"), *climbing stairs* ("Treppen steigen"), and *sleeping/resting and sitting* ("Schlafen/Ruhen und Sitzen"). In each domain variations between seasons (summer/winter), single months or weekday and weekend were considered, and information on activity intensity was collected.
The questionnaire was completed by each participant during the measurement in the respiration chamber. After evaluation by the Heidelberger researchers, a set of variables was provided of which the following parameters were derived and used for analysis:

- *Time [hours/week] and intensity [MET-hours/week] in occupation*
- *Time [hours/week] in locomotion (by foot, by bicycle)*
- *Time [hours/week] and intensity [MET-hours/week] in domestic work and gardening*
- *Time [hours/week] and intensity [MET-hours/week] in leisure time bicycling*
- *Time [hours/week] in leisure time walking*
- *Time [hours/week] in sports/exercise*
- *Time [hours/day] spent sitting*
- *Time [hours/day] spent sitting on weekdays*
- *Time [hours/day] spent sitting on weekend*
- *Time [hours/day] spent sleeping excluding napping*
- *Time [hours/day] spent sleeping including napping*

Missing values in any parameter were considered as ‘zero’ in the calculation, assuming that participants intentionally left blank, if they don’t spent time in the activity of question. Based on this provided set, additional parameters were derived by adding up several domains:

- *Total time in locomotion, bicycling, walking, sports [hours/week]*
- *Total time in locomotion, bicycling, walking, sports, domestic work [hours/week]*
- *Total time in occupation, locomotion, bicycling, walking, sports, domestic work [hours/week]*

4.2.3.11 Dietary record

Information about macro- and micronutrient consumption was determined with a dietary record. The dietary record listed 197 items of common foods and drinks and a conventional portion size for each item (e.g. item: ‘bread’, portion size: ‘1 slice’). The participants were instructed to use the given portion size and making tally sheets when the item was consumed or, alternatively, to write down weighed portions. If foods or drinks not included in the item list were consumed, the participants were instructed to add these individual items and the consumed portion size in the dietary record. Missing or unclear information were resolved in conversation with the participant at the second study center visit. The participants were asked to keep the dietary record for at least 7 consecutive days during the 2-week examination period to get an reliable overview of their eating habits [214].

The dietary records were analyzed using the software Optidiet (V5.0.2.010, GOE mbH, Linden, Germany) that is based on the nutritional content of food provided by the German Nutrient Database (“Bundeslebensmittelschlüssel”). The average daily energy intake and the average daily consumption of macronutrients (carbohydrates, proteins, fats), micronutrients (vitamins, minerals) and ‘special nutrients’ (water, dietary fiber, alcohol, cholesterol, sucrose, saturated fatty acids, omega-3- and omega-6-fatty acids) was provided by the software. For macronutrients, fatty acids and sucrose the relative energy intake based on total energy intake was calculated additionally by the software.

For analysis, the following parameters were derived:

- *(Total) energy intake [kilocalories per day]*
- *Fat intake [grams per day]*
- *Relative fat intake [percent of total energy intake]*
- *Carbohydrate intake [grams per day]*
- *Relative carbohydrate intake [percent of total energy intake]*
- *Protein intake [grams per day]*
- *Relative protein intake [percent of total energy intake]*

4.2.3.12 Intake of medical drugs and dietary supplements

At the first study center visit, information about regular or occasional intake of medical drugs and dietary supplements during the previous seven days was collected using IDOM software, which is a database-assisted instrument for drug ascertainment. To enable correct identification, information of central pharmaceutical number ("Pharmazentralnummer, PZN"), drug name, manufacturer, dose, and/or box size was needed, which was collected from drug packing, patient information leaflet, participant's self-statement or retrospective assessment by questionnaire. Participants who took drugs interfering with relevant outcome variables (energy expenditure, blood parameters) were considered in sensitivity analyses.

4.2.3.13 Standardized activity program

At the first study center visit, after initialization of the accelerometers the participants performed a standardized activity program in order to analyze patterns of accelerometer signals for specific activities. In the framework of this thesis, the results of this examination were not considered.

4.2.3.14 Deviations from study protocol

The following minor deviations from study protocol had occurred during examination:

- When the DLW method was performed (paragraph 4.2.3.2), one participant collected the basal urine sample at home in the afternoon (instead of collecting the basal urine sample in the morning at the study center), one participant didn't go to sleep after consuming the DLW dose, but stayed awake during the night without any consumption of food or drinks (shift worker), and one participant forgot to collect the fourth urine sample on day 9 in the evening. None of these deviations affected the measurement of TEE.
- When accelerometry over 14 days was performed (paragraph 4.2.3.3), two participants missed to change the accelerometers correctly on day 8, but did it instead delayed on day 9. The missing of accelerometry data due to delayed change of accelerometer devices was considered in the analysis. As a consequence for all future measurements, the recording period of the first accelerometer device was extended for 24 hours (until day 9 at 23.59 h). Hence, the overlap of the recording period of the two accelerometer devices was extended to day 8 and day 9.
- When ADP was performed using BOD POD® (paragraph 4.2.3.4), for technical reasons in four cases the measurement had to be performed at the second study center visit and not

at the first one. Since all participants were stable in weight during the examination period, no changes in body composition were expected either.

- When blood pressure was determined (paragraph 4.2.3.5), in eight cases, despite upper arm circumference was >32 cm, the normal size cuff was used, because the big size cuff didn't fit in length. This may have led to measurement errors with falsely elevated values for systolic and diastolic blood pressure [215].
- When blood samples were taken and processed (paragraph 4.2.3.7), in three cases the tourniquet was put on longer than one minute to fill the tubes (instead of releasing the tourniquet after selection of puncture site and not exceeding one minute), in five cases the recommended order of draw for serum and EDTA-plasma monovettes was altered so the risk of carry-over anticoagulants was not avoided, and in one case the specified dwell time was exceeded during blood sample processing. It is assumed that these minor deviations did not affect the results of the blood parameter measurement.
- When nitrogen excretion rate was determined for REE calculation (paragraph 4.2.3.8), for one male participant no urine samples could be collected. This missing value was imputed with the sex-specific mean of resting nitrogen excretion rate of the remaining 24 male participants.

4.3 Statistical analysis of ActivE study data

Statistical analyses were performed using the software package SAS Enterprise Guide, version 4.3 (SAS Institute Inc., Cary, NC, USA). Additional calculations of accelerometer-derived activity parameters were performed using the ActiLife software (ActiGraph LLC., Pensacola, FL, USA). Statistical tests were two-tailed and corresponding p-values were considered statistically significant if $p<0.05$.

4.3.1 Calculation of activity parameters derived from accelerometry data

Physical activity (PA) parameters were calculated automatically along with the download (paragraph 4.2.3.3), and subsequently using ActiLife software (version 6.11.9). To calculate the daily duration spent in defined PA intensity categories, an adapted version of the implemented 'Freedson Adult VM3 (2011)' algorithm was used. Based on *Vector magnitude (VM) counts per minute*, the default 'Freedson Adult VM3 (2011)' algorithm defined PA intensity categories as 'light' (0 – 2689 cpm), 'moderate' (2690 – 6166 cpm), 'vigorous' (6167 – 9642 cpm) and 'very vigorous' (≥ 9643 cpm) [139]. In the adapted algorithm the categories 'vigorous' and 'very vigorous' were merged to one category called 'vigorous' (≥ 6167 cpm), and the category 'light'

was split into the categories 'inactive' (0 – 78 cpm) and 'low' (79 – 2689 cpm) to distinguish between periods of low activity and periods of (nearly) no activity (**Figure 4-3**). The self-defined cutoff of 78 cpm was derived from the 95th percentile of the distribution of participants' average *VM counts per minute* during sleeping periods (based on documentation in the diary) where nearly no activity was assumed.

Default 'Freedson Adult VM3 (2011)'	**Light**		**Moderate**	**Vigorous**	**Very vigorous**
	0 - 2689 cpm		2690 - 6166 cpm	6167 - 9642 cpm	≥ 9643 cpm
Adapted 'Freedson Adult VM3 (2011)'	**Inactive**	**Low**	**Moderate**	**Vigorous**	
	0 - 78 cpm	79 - 2689 cpm	2690 - 6166 cpm	≥ 6167 cpm	

Figure 4-3 Classification of physical activity intensity categories based on Vector magnitude counts according to default 'Freedson Adult VM3 (2011)' algorithm and the adapted algorithm.
cpm counts per minute.

For each of the 13 days, PA parameters were provided by the software. For analysis, the arithmetic mean of days 2 to 14 was calculated of the following PA parameters of interest:

- *Vector magnitude counts [counts per minute]*
- *Axis 1 counts [counts per minute]*
- *Axis 2 counts [counts per minute]*
- *Axis 3 counts [counts per minute]*
- *Steps per day*
- *Steps per minute*
- *Time in inactivity [minutes per day]*
- *Time in low PA [minutes per day]*
- *Time in moderate PA [minutes per day]*
- *Time in vigorous PA [minutes per day]*
- *Time in moderate to vigorous PA [minutes per day]*

Additionally, the time spent in PA with low, moderate and vigorous intensity was summed up to derive the daily average of *time in total activity*, and –based on that parameter– to calculate the relative proportion of time spent in low, moderate and vigorous PA.

- *Time in total activity [minutes per day]*
- *Proportion of time in low PA [% of time in total activity]*
- *Proportion of time in moderate PA [% of time in total activity]*
- *Proportion of time in vigorous PA [% of time in total activity]*

To investigate potential mutual associations between accelerometer-derived activity parameters a Spearman rank correlation analysis was conducted.

4.3.2 Calculation of AEE

Activity-related energy expenditure (AEE) was calculated using the daily average of total energy expenditure (TEE) measured by doubly-labeled water, and resting energy expenditure (REE) measured by indirect calorimetry in a respiratory chamber. Diet-induced thermogenesis was defined as 10 % of TEE [57].

$$AEE\ [kcal/d] = TEE\ [kcal/d] - REE\ [kcal/d] - 0.1*TEE \quad \text{(Eq. 14)}$$

To investigate potential mutual associations between AEE, accelerometer-derived activity parameters and other potential predictor variables a Spearman rank correlation analysis was conducted.

4.3.3 Characteristics of the ActivE study population

Prior to analyses, all parameters were checked for plausibility (minimum, maximum, negative values) and distribution (histogram, QQ-plot). If not specified otherwise, continuous variables were described as arithmetic mean, standard deviation, minimum and maximum value, or in case of non-normal distribution as median, 25^{th} and 75^{th} percentile. Categorical variables were described as absolute number and percentage based on total number for men or women. Differences between men and women were determined using t-test, Mann-Whitney-U test or chi-square test in case of normally distributed continuous, non-normally distributed continuous or categorical variables, respectively.

4.3.4 Development of AEE prediction models

4.3.4.1 Exclusion of observations

One participant was excluded from this part of analysis because of abnormal thyroid hormone blood levels that became apparent during the examination period, which implies potential adverse effects for the results of the energy expenditure measurements methods (DLW, respiration chamber). Thus, the analytic sample size for the development of prediction models for DLW-derived AEE and corresponding association analyses was reduced to 49 observations.

4.3.4.2 Variable selection strategy

AEE prediction models were developed using linear regression analysis (*PROC REG* procedure in SAS). Due to the high number (>200) of potential candidate variables in contrast to 49 observations, a multi-step selection process was carried out as illustrated in **Figure 4-4**.

First, variables with missing values and redundant variables originated from further calculations, mathematical conversions or repeated measurements (e.g. from second study center visit) were not considered. Second, the remaining 76 variables were grouped with regard to context or examination module.

The group of accelerometer-derived parameters was considered separately. Within this group, each single parameter was regressed on AEE to find out which parameter is most appropriate for AEE prediction (conceptual-based variable preselection).

Within each of the other variable groups, significant variables were selected using stepwise selection regression on AEE with p-value limits of both 0.05 and 0.1 for the corresponding partial F-statistic for including and retaining the variables (statistical-based variable preselection). Each preselected variable was considered for the subsequent main-selection step.

Further, the crude association of each preselected variable with AEE was assessed using simple linear regression, combined with checking for normal distribution and homoscedasticity of variance in the residuals (histogram, QQ-plot, scatterplot of residuals vs. predicted values) [216]. If the residuals had an apparent trend or deviated distribution, the variable was adequately transformed. Further, the range of values was checked in order to avoid computational inaccuracies or modeling problems due to improper scaling of the variables [217].

Next, based on the conceptual-based selection of accelerometer-derived parameters and the statistical-based selection of additional variables in defined variable groups, two-parameter models were calculated to determine how much variance of AEE can be explained by one accelerometer-derived parameter and one additional parameter using linear regression.

Finally, the main-selection step was performed using stepwise selection regression and taking all preselected variables into account, but separate for each accelerometer-derived physical activity parameter. Six different combinations of p-value limits of the partial F-statistic for including/retaining variables were applied to create prediction models: (a) 0.05/0.05, (b) 0.10/0.10, (c) 0.25/0.25, (d) 0.50/0.05, (e) 0.50/0.10, (f) 0.50/0.25.

Final models were selected applying two approaches: On the one hand, models with p-value combinations (a) and (d) were selected (= Model A). These models contain only predictor

variables that meet the p-value threshold of <0.05 for the corresponding t-test statistic, where the regression coefficient estimator is equal to zero (null hypothesis).

On the other hand, additional models were selected by means of the Schwarz Bayesian Information Criterion (SBC) [218], that is a maximum likelihood-based model fit criterion penalizing for numbers of model parameters to avoid overfitting [219]. The criterion can be used for model selection or comparison of models, where smaller SBC values represent better fitted models compared to other obtained models from the same data set [219, 220]. In this analysis, every model that emerged during the single steps of the stepwise selection process of each p-value combination (a) to (f) and revealed a lower SBC compared to Model A was additionally selected as Model B. These additional models could include predictor variables that do not necessarily meet the p-value threshold of <0.05 for the corresponding t-test statistic.

For each developed prediction model, the estimated regression coefficients (unstandardized and standardized), standard errors, p-values and partial R^2 of the predictor variables were provided, as well as the unadjusted and adjusted coefficients of determination (R^2), and the SBC criterion of the model.

4.3.4.3 Alternative models with reduced variable sets

Additionally, alternative models were developed simulating that only a smaller set of predictive variables was available (e.g. due to potentially not implemented or missing measurements in a study). Therefore, the main selection step was repeated for various reduced sets of preselected variables, of which the following sets were investigated:

- No ADP measurement
- No ADP & BIA (i.e. no information about body composition)

- No QUAP
- No IPAQ
- No IPAQ & QUAP (i.e. no additional information about PA from questionnaires)

- No IPAQ & QUAP & ADP
- No IPAQ & QUAP & ADP & BIA

- No Nutrition
- No Nutrition & QUAP
- No Nutrition & IPAQ

- No Nutrition & IPAQ & QUAP

- No Nutrition & IPAQ & QUAP & ADP
- No Nutrition & IPAQ & QUAP & ADP & BIA
- No Nutrition & QUAP & ADP

For each variable set the main-selection step was performed, as described above, to develop one model based on stepwise selection with predictors meeting the p-value threshold of <0.05 (Model A), and - if applicable - an additional model that yielded an improved (lower) SBC criterion during the stepwise selection process (Model B).

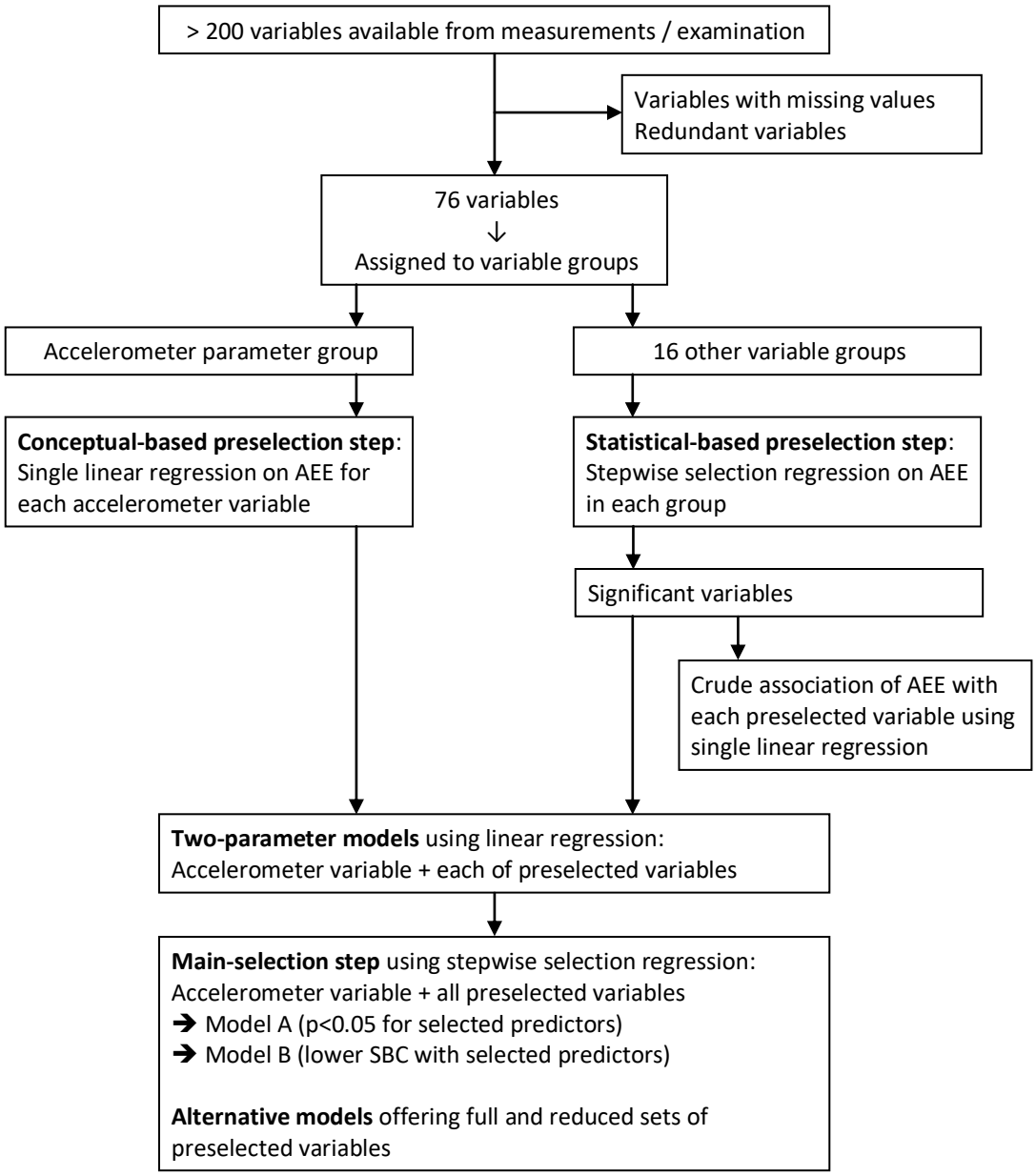

Figure 4-4 Variable selection strategy for the development of AEE prediction models

4.3.4.4 Regression diagnostics and sensitivity analyses

All developed Models A and B were checked for multicollinearity (determined by the variance inflation factor (VIF) of the predictors, and the intercept adjusted condition number of the total model) [217], as well as for fulfilment of regression assumptions, which includes normal distribution of residuals (verified graphically with histograms and QQ-plots of the residuals), and homoscedasticity (verified graphically with scatterplots of residuals vs. predicted values) [216].

Further, all models were checked for influential observations by evaluating the following diagnostic statistics implemented in SAS: studentized residuals, leverages, Cook's distance, Dffits, Dfbetas of predictors (Appendix **Table 10-3**) [217, 220]. Observations that apparently exceeded the recommended cutoffs of one or more of these diagnostic measures were investigated in detail.

In sensitivity analyses, models were recalculated after excluding influential observations. The change in unstandardized regression coefficients was determined by calculating the ratio of the absolute regression coefficients difference (|beta of predictor$_{all\ observations}$ – beta of predictor$_{after\ exclusion}$|) to the standard error of the regression coefficient (SE of beta of predictor$_{all\ observations}$).

To assess the robustness of the final AEE prediction models [221, 222], all models were recalculated in full and reduced variable sets with different variable selection techniques (forward selection and backward elimination in linear regression using *PROC REG* procedure in SAS, and LASSO selection [223] with optimized SBC criterion using *PROC GLMSELECT* procedure in SAS) starting from the main-selection step, where all preselected variables were taken into account, but separately for each accelerometer-derived activity parameter.

Further, applying the bootstrap approach [224-226], 2000 bootstrap samples of same size (n_b=49) were drawn with replacement from the initial study sample (n=49). Each bootstrap sample passed through the main-selection step applying (1) stepwise selection in linear regression, as described above, and (2) LASSO selection with optimized SBC criterion to create AEE prediction models in full and reduced variable sets. The relative frequency with which variables were selected was calculated. Selection frequencies of 60 % and above were considered as important [226, 227].

4.3.5 Association of physical activity duration and intensity with cardiometabolic factors

To investigate the association of duration and intensity of physical activity (PA) with factors of inflammation and glucose and lipid metabolism, partial Spearman rank correlation (adjusted for sex and age) and linear regression analysis were performed, fitting blood levels of *(total) cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, cholesterol-HDL-ratio, glucose, insulin, HbA_{1c}, C-peptide, HOMA index* and *CRP* as outcome variables, and accelerometer-derived activity parameters *time in low PA*, *time in moderate PA*, *time in vigorous PA*, *time in total activity* as independent variables (paragraph 4.3.1). To fulfil the assumptions of regression residuals (normal distribution with mean of zero, homoscedasticity), the factors *triglycerides, insulin, HOMA index* and *CRP* were *Log*-transformed. To examine the independent association of activity parameters with cardiometabolic factors, multiple linear regression with mutual adjustment was performed, fitting each cardiometabolic factor with *time in low PA, time in moderate PA*, and *time in vigorous PA* (combination A); and *time in total activity, proportion in moderate PA*, and *proportion in vigorous PA* (combination B).

All models were adjusted for age, sex, BMI, smoking status (included as dummy variable, reference = never smokers) and alcohol consumption (derived from dietary record in g/day) as potential confounders. For each model, the unstandardized regression coefficients and 95% confidence intervals for the activity parameters were presented. Units of the 'absolute' activity parameters *time in total activity, time in low PA, time in moderate PA* and *time in vigorous PA* were converted in '30 minutes per day' (instead of 'minutes per day'). To examine whether nonlinearity was present, a quadratic term of each activity parameter was added to the model and checked for significant contribution; but nonlinearity was not observed.

Additionally, sensitivity analyses were conducted to examine the robustness of the results when several issues were considered. First, participants taking medication that affect the concentration of the blood parameters (e.g. statins affect factors of lipid metabolism and CRP concentration) were excluded from the analysis. Second, according to the recommendations of the American Heart Association/Centers for Disease Control and Prevention (AHA/CDC) with respect to investigations of CRP [228], participants with CRP levels >10 mg/l were excluded from the analysis. Third, all models were checked for influential observations by evaluating diagnostic statistics (studentized residuals, leverages, Cook's distance, Dfbetas of activity parameters) [217, 220]. Observations that exceeded the recommended cutoffs of one or more diagnostic measures were investigated in detail and excluded from the analysis (Appendix **Table 10-3**).

4.3.6 **Association of AEE with cardiometabolic factors**

Analog to the association analysis between physical activity parameters and cardiometabolic factors, in another approach AEE was investigated as independent variable and its association with cardiometabolic factors using linear regression models. As described in the previous paragraph, the same cardiometabolic factors were used as outcome variables in separate models and the same transformations and regression checks were conducted (paragraph 4.3.5). In separate models, the independent variable AEE was included as (1) measured AEE derived from DLW method, and (2) predicted AEE calculated from two different prediction models, which were developed from ActivE study data.

The association between AEE and each cardiometabolic factor was calculated in crude (including only AEE variable) and adjusted models (including AEE variable and the adjusting factors sex, age, BMI, smoking status and alcohol consumption). For each model, the estimated regression coefficients and 95% confidence intervals for the AEE parameters were provided.

5 Results

5.1 Systematic review on prediction of activity-related energy expenditure based on accelerometer-derived physical activity under free-living conditions

5.1.1 Search results and study selection[5]

The search in MEDLINE resulted in a total of 299 articles (**Figure 5-1**). After reading abstracts (235 articles excluded) and full texts (43 articles excluded), 21 articles met the inclusion criteria. After screening reference lists of these articles and relevant on-topic reviews, 16 additional articles were identified to fulfill the inclusion criteria. Of these 37 articles, 19 articles examined the association of accelerometry-derived physical activity output and DLW-derived AEE, and 18 articles aimed at validation of the accelerometer device by comparing accelerometer-derived AEE and DLW-derived AEE; latter were excluded for the analysis.

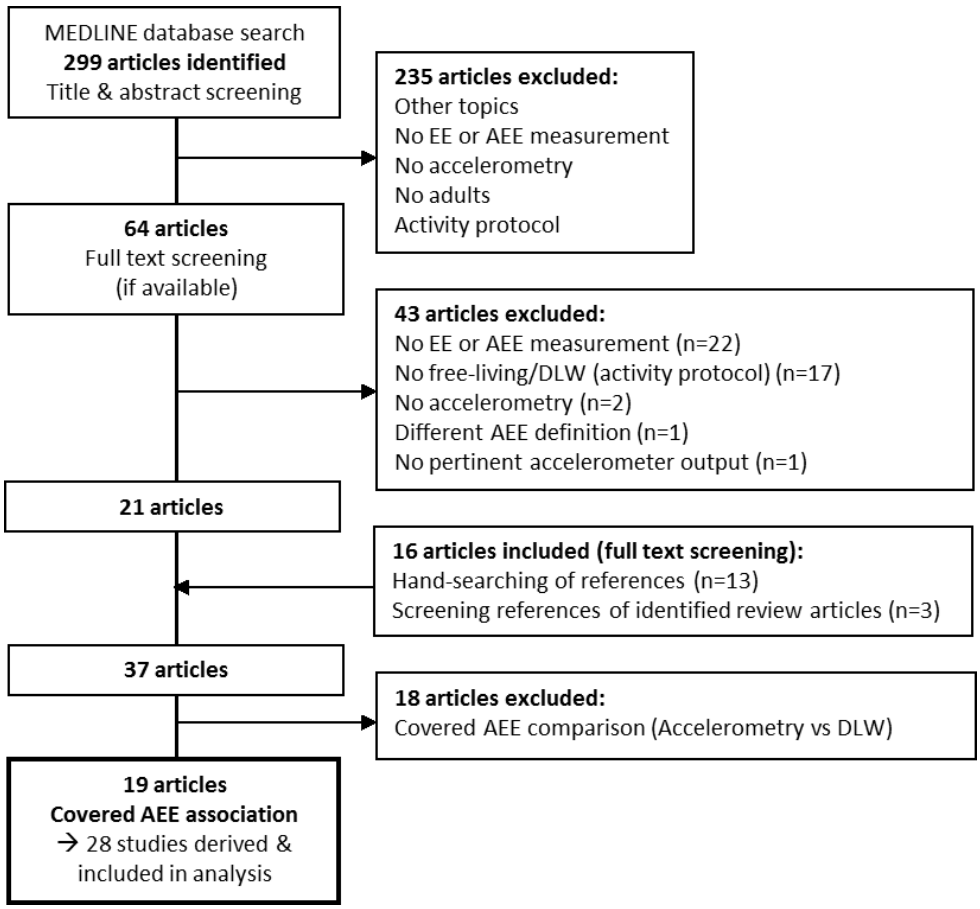

Figure 5-1 Flowchart of article selection.[6]
AEE activity-related energy expenditure, DLW doubly-labeled water.

[5] In the framework of this thesis, parts of the results on "Search results and study selection" have already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197. (see Appendix Figure 10-4 for updated search results)

[6] In the framework of this thesis, this figure has already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

5.1.2 **Characteristics of included articles**[7]

Out of the 19 included articles, 28 separate studies were derived due to application of multiple accelerometers [90, 181-183] and investigation of several population subgroups [39] described in one article. Further, of these 28 studies, 10 studies not only reported on the association between accelerometer output and DLW-derived AEE, but investigated additional factors beyond accelerometry to predict AEE.

The characteristics of the 19 included articles are presented in **Table 10-4** (Appendix), and a summary of the study characteristics of the derived 28 studies is given in **Table 5-1**. All studies were of cross-sectional design. The sample size ranged from 10 to 149 individuals, which were in most studies (n=20) drawn from the general population. A total of 19 different accelerometer devices from 15 different manufacturers were applied, of which 7 accelerometers were of uniaxial type, 11 accelerometers were of triaxial type and 1 accelerometer of biaxial type.

Uniaxial accelerometers were used in 12 studies, triaxial accelerometers were used in 15 studies, and biaxial accelerometers in 1 study (**Table 5-1**). In most studies the accelerometer was placed at the trunk (particularly at the hip, lower back, waist or chest), and wear time was restricted to waking hours (**Table 5-1**). The duration of recording accelerometer data ranged from 5 to 15 days. Most studies (n=16) reported counts per time interval (i.e. counts per day, counts per minute) as accelerometer output metric (**Table 5-1**). Using the DLW method, TEE was measured over a period of at least 7 days up to 14 days. In most studies resting, basal or sleeping metabolic rate was measured with indirect calorimetry techniques (ventilated hood, handheld mask, respiration chamber), whereas only a few studies estimated this EE component with common prediction formulas (Appendix **Table 10-4**) [189, 190, 193].

[7] In the framework of this thesis, parts of the results on "Characteristics of included articles" have already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

Table 5-1 Summary of characteristics concerning study population, accelerometer, and prediction model for all studies and subset of studies with additional prediction model (derived from articles in Table 10-4)[8]

		All studies (n=28)	Studies with additional prediction model (n=10)[a]
Study population[b]	general population	20	8
	military personnel, soldiers	2	2
	patients	7	0
Sample size	≤ 15	5	1
	16 – 50	16	6
	51 – 100	5	1
	> 100	2	2
Sex	male & female	21	6
	female only	6	3
	male only	1	1
Age range	< 40 years	12	6
	> 40 years	10	1
	overall age range (ca. 20 – 70 years)	6	3
Applied Acc type	uniaxial	12	4
	triaxial	15	6
	biaxial	1[c]	0
Acc recording period	≤ 1 week	12	5
	> 1 week	16	5
Acc body position	trunk (lower back, hip, waist, chest)	20[c]	7
	limbs (wrist, upper arm, ankle, thigh)	8[c]	3
Acc wear time	waking hours	21[c]	6
	24 hours	7	4
Acc output metric	Counts per time interval	16	6
	Steps per time interval	6	1
	acceleration	3	2
	other	3	1
Acc output type[d]	uniaxial output	15	6
	triaxial output	13	4
Analysis approach: association/ prediction model	linear (Pearson correlation, linear regression)	22	9
	non-linear (Spearman correlation, log linear regression)	4	1
	both	2	0

Values are number of studies. [a] Not including studies of *Pomeroy et al*. [182] [b] For *Skipworth et al*. [229]: this study was allocated to two categories, 'general population' and 'patients'. [c] Missing information in *Adams et al*. [193] and *Colbert et al*. [90] was substituted by making the following assumptions based on other references that used the same accelerometer device; for *Adams et al*. [193]: Acc body position = trunk, Acc wear time = waking hours; for *Colbert et al*. [90] (SenseWear Pro3): Acc type = biaxial, Acc body position = limbs. [d] This variable combines information from Acc type and Acc output metric; steps output from biaxial or triaxial devices were assigned to 'uniaxial output'. Acc accelerometer.

[8] In the framework of this thesis, this table has already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

5.1.3 **Crude explained variance (R^2) and its relation to study characteristics**[9]

In this systematic review studies applied linear approaches (Pearson correlation, linear regression) and nonlinear approaches (Spearman rank correlation, log-linear regression) to investigate the association between accelerometer output and DLW-derived AEE (**Table 5-1**). In the meta-regression analysis 24 studies were considered, since in 4 studies no information about crude R^2 was available. Crude R^2 ranged from 0.043 to 0.80 (**Table 10-4**) with a median of 0.26 (**Figure 5-2**). Crude R^2 did not significantly differ by accelerometer recording period (≤1 week vs >1 week), body position (trunk vs limbs), wear time (waking hours vs 24 hours), accelerometer output type (uniaxial vs triaxial outputs), or accelerometer output metrics (counts vs steps vs other) (all p-values of Mann-Whitney U-test and Kruskal-Wallis test >0.05, **Figure 5-2**). Further, crude R^2 was inverse associated with sample size ($r_{Spearman}$ = -0.45, p=0.03, **Figure 5-3**), but not associated with population's mean age ($r_{Spearman}$ = 0.16, p=0.44, **Figure 5-3**).

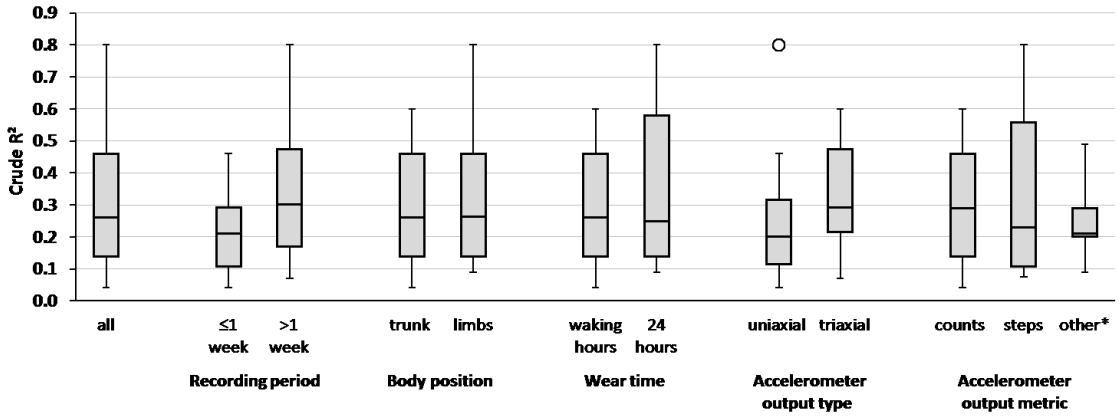

Figure 5-2 Crude R^2 for all studies (n=24), and stratified by accelerometer characteristics. [10]
* includes the categories 'acceleration' and 'other' listed in Table 5-1. Circle = outlier.

[9] In the framework of this thesis, parts of the results on "Crude explained variance (R^2) and its relation to study characteristics" have already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

[10] In the framework of this thesis, this figure has already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

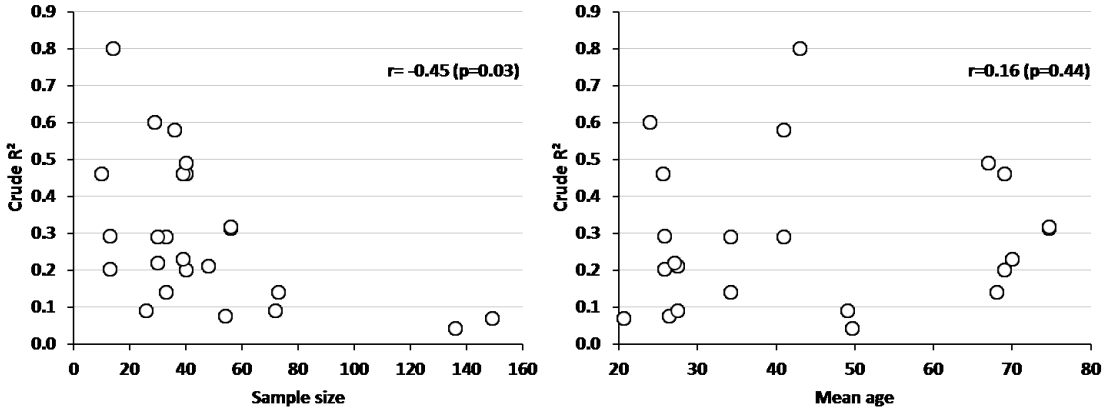

Figure 5-3 Scatterplots of crude R^2 and sample size or population's mean age (n=24 studies).[11]

5.1.4 Explained variance (R^2) in studies with additional predictors beyond accelerometer output[12]

Ten studies not only investigated the crude association between accelerometer output and DLW-derived AEE, but included additional factors to improve the prediction of AEE. These 10 studies were of similar characteristics according to study population and accelerometer features compared to all 28 studies (**Table 5-1**). Details of the prediction models are presented in **Table 5-2** and summarized in **Table 5-3**. Since the studies of *Pomeroy et al.* [182] reported no information about crude R^2 and total R^2, they were not considered in the summary tables (**Table 5-1**, **Table 5-3**) and were excluded from the analysis.

To improve the explained variance of AEE when only accelerometer output is in the model, studies included 1, 2 or 3 additional predictors in the prediction model. Weight and fat-free mass were the most frequently added predictors (**Table 5-3**). In the multivariate models, the explained variance of AEE (total R^2) ranged from 0.125 to 0.86 (median 0.41), and partial R^2 for accelerometer output ranged from 0.04 to 0.41 (**Table 5-2**). Four studies presented several models with either fat-free mass or weight as predictors [185-188]. Interestingly, those models that included fat-free mass explained a higher proportion of variance in AEE compared with the models that included weight instead.

[11] In the framework of this thesis, this figure has already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

[12] In the framework of this thesis, parts of the results on "Explained variance (R^2) in studies with additional predictors beyond accelerometry" have already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

Stratifying the 10 studies by number of additional predictors, total R^2 did not differ between studies when 1 predictor (n=4, median total R^2=0.42), 2 predictors (n=4, median total R^2=0.37) or 3 predictors (n=2, median total R^2=0.63; p=0.56) were included additionally to accelerometer output. Further, total R^2 was inversely correlated with sample size, similar to the crude R^2 relation, but without statistical significance ($r_{Spearman}$ = -0.53, p=0.12).

Eight studies were available to investigate the improvement of R^2 when further predictors were included in addition to accelerometer output, since they reported information in crude R^2 (with accelerometer output but no additional predictors) and total R^2 (with accelerometer output and additional predictors, **Figure 5-4**) [39, 184, 185, 187-189, 191]. In 3 studies 1 additional predictor was included improving R^2 from 0.21 to 0.31 (p=0.25). In 3 studies 2 additional predictors were included improving R^2 from 0.08 to 0.33 (p=0.25), and in 2 studies 3 additional predictors were included improving R^2 from 0.37 to 0.63 (p=0.50). The (median) improvement of R^2 did not differ by number of additional predictors (p=0.16). However, taking all 8 studies together, R^2 improved significantly from 0.16 without additional predictors to 0.37 with the corresponding number of additional predictors (p=0.008, **Figure 5-4**).

Table 5-2 Additional study characteristics and effects of added predictors on total R^2 in subset of studies with prediction model (n=10)[13]

Reference	**Crude R^2** (Acc-output vs. AEE [*abs*] or AEE/kg [*rel*])[a] **Analytic sample size (n)** *(from Table 10-4)*	**Prediction model** Analysis approach	**Predictors of final model(s)** best model in bold	**Total-R^2** (predictors vs. AEE [*abs*] or AEE/kg [*rel*])[a] **Partial-R^2** (for Acc-output)	**Other factors** not included in final model
Horner *et al.* (2013) [189]	R^2=0.07 (vs. log AEE) (n=149)	Log linear regression	*Log* counts per day, height, sex (stratified)	$_{abs}R^2$= 0.41 $_{abs}$Partial-R^2=0.06	Weight
Tudor-Locke *et al.* (2012) [191]	$_{abs}R^2$=0.0752 (n=54)	Pearson correlation, Linear regression	Steps per day, peak 30min cadence (steps per min), time in cadence band	$_{abs}R^2$=0.33	Age, height, BMI, weight
Kinnunen *et al.* (2012) [190]	NS (n=22)	Linear regression (stepwise)	Normalized hand movement per min, weight, height	$_{rel}R^2$=0.74 $_{rel}$**adj.R^2=0.70** $_{rel}$Partial-R^2=0.41	
van Hees *et al.* (2011) [39]	$_{abs}R^2$=0.21 $_{rel}R^2$=0.27[b] (n=48)	Linear regression	**(1) VM-acceleration, weight** (2) VM-acceleration, body site, body site*VM-acceleration	**(1)** $_{abs}$**R^2=0.31** (2) $_{abs}R^2$=0.18	Height, age, arm length; squared VM-acceleration
	$_{abs}R^2$=0.09 $_{rel}R^2$=0.05[b] (n=26)	Linear regression	(1) VM-acceleration, weight **(2) VM-acceleration, body site, body site*VM-acceleration**	(1) $_{abs}R^2$=0.05 **(2)** $_{abs}$**R^2=0.19**	
Bonomi *et al.* (2010) [185]	$_{abs}R^2$=0.29 $_{rel}R^2$=0.50 (n=30)	Linear regression (stepwise)	(1) Counts per day, weight **(2) Counts per day, FFM**	(1) $_{abs}R^2$=0.46; Partial-R^2=0.16 **(2)** $_{abs}$**R^2=0.53**; Partial-R^2=0.23	1) Height, age, sex 2) FM, age, sex
Bonomi *et al.* (2009) [186]	NS (n=15)	Linear regression (stepwise)	(1) Counts per day, weight **(2) Counts per day, FFM**	(1) $_{abs}R^2$=0.47; Partial-R^2=0.21 **(2)** $_{abs}$**R^2=0.60**; Partial-R^2=0.38	1) Height, age, sex 2) FM, age, sex
Assah *et al.* (2009) [184]	$_{rel}R^2$=0.14 (n=33)	Linear regression	Counts per day + (1) urban/rural (2) age, sex **(3) age, sex, urban/rural** (4) age, sex, body fat% (5) age, sex, body fat%, urban/rural	$_{rel}R^2$= (1) 0.21 (2) 0.34 **(3) 0.40** (4) 0.35 (5) 0.40	
Plasqui *et al.* (2005) [188]	$_{rel}R^2$=0.60 (n=29)	Linear regression	(1) VM-counts per day, age, height, weight **(2) VM-counts per day, age, FFM, FM** (3) Vertical-counts per day, age, height, weight	(1) $_{abs}R^2$=0.81; $_{abs}$Partial-R^2=0.33 **(2)** $_{abs}$**R^2=0.86** (3) $_{abs}R^2$=0.77	
Mâsse *et al.* (2004) [187]	$_{abs}R^2$=0.043 (n=136)	Pearson correlation, Linear regression	(1) Counts per day, weight **(2) Counts per day, FFM**	(1) $_{abs}R^2$=0.092; Partial-R^2=0.05 **(2)** $_{abs}$**R^2=0.125**; Partial-R^2=0.04	
Pomeroy *et al.* (2011)[c] [182]	NS (n=50)	(Spearman correlation)	NS (partial for age, sex, height)	$_{abs}$Partial-R^2=0.22 (Actigraph MTI)	
		Linear regression	NS (partial for age, sex, height)	$_{abs}$Partial-R^2=0.18 (Dynastream AMP-331)	

[a] In the model, the dependent AEE variable was considered as absolute [abs] or relative [rel] measure. [b] Data were obtained from supplement information of the article. [c] This article only reported values for partial R^2 and was therefore not taken into account in the analysis and summary tables. Acc accelerometer, adj. adjusted, AEE activity-related energy expenditure, BMI body mass index, FFM fat-free mass, FM fat mass, NS not stated, VM vector magnitude.

[13] In the framework of this thesis, this table has already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

Table 5-3 Summary of characteristics concerning additional predictors for studies with additional prediction model (derived from articles in Table 5-2)[14]

		Studies with additional prediction model (n=10)[a]
Additional predictors[b]	Sex	2
	Age	2
	Height	3
	Weight	7
	Fat-free mass	4
	Body fat	2
	Other	4
Number of additional predictors (best model)[c]	1	4
	2	4
	3	2
Partial R^2 for accelerometer output (best model)[c]	NS	4
	0.00 – 0.20	2
	0.21 – 0.40	3
	0.41 – 0.60	1
	0.61 – 0.80	0
	> 0.80	0

Values are number of studies. [a] Not including studies of *Pomeroy et al.* [182] [b] Allocation to more than one category was possible because of various developed models. [c] In studies with various models the best model was selected (defined as having greatest total R^2 along with lowest number of predictors). NS not stated.

[14] In the framework of this thesis, this table has already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

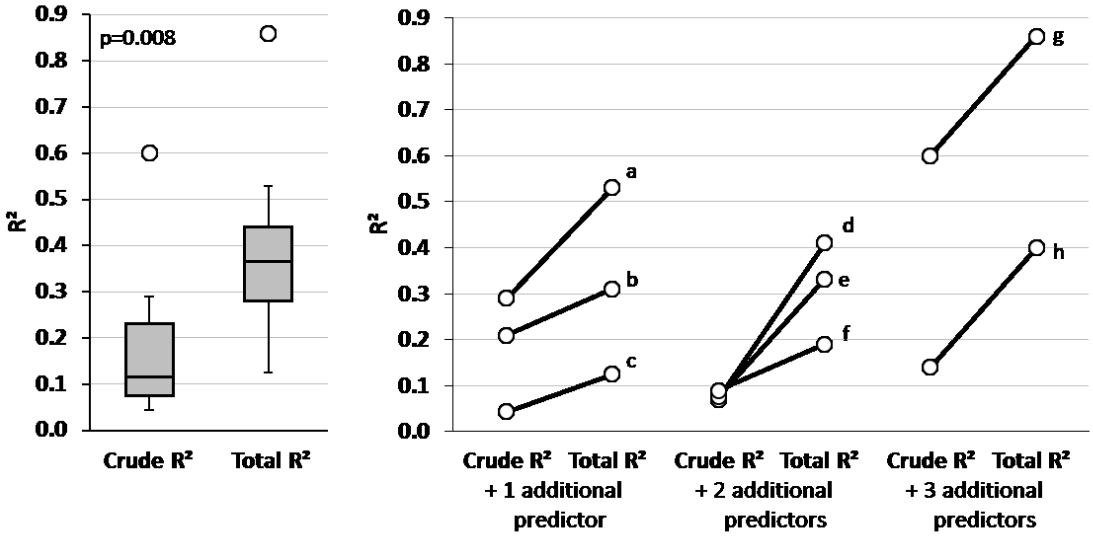

Figure 5-4 Crude R^2 and total R^2 for subset of studies that included additional predictors to accelerometer output (n=8) combined for all studies (**left**), and stratified by number of additional predictors (**right**).
Included additional predictors: (a) fat-free mass, (b) weight, (c) fat-free mass, (d) height, sex, (e) peak cadence, time in cadence band, (f) body site, interaction term, (g) age, fat-free mass, fat mass, (h) age, rural/urban, sex (Table 5-2). [15]

5.1.5 Sensitivity analysis considering AEE as absolute or relative measure[16]

Of the 24 studies that were available for analysis, 11 studies investigated AEE only as absolute measure [181, 183, 187, 189, 191], 6 studies investigated AEE only relative to body weight (AEE per kg) [184, 188, 192, 193, 229, 230], and 7 studies investigated AEE as both absolute and relative measure [39, 90, 185, 194, 195]. Crude R^2 did not differ between the groups of studies using (absolute) AEE and studies using (relative) AEE per kg when analyzed as between-group comparison (*AEE studies*: n=18, crude R^2 range 0.043 – 0.49, median 0.23; *AEE per kg studies*: n=13, crude R^2 range 0.05 – 0.80, median 0.35; p=0.09) or as within-group comparison (n=7, *AEE studies*: crude R^2 range 0.09 – 0.46, median 0.29; *AEE per kg studies*: crude R^2 range 0.05 – 0.62, median 0.35; p=0.08). Similar to the main analysis, in both groups of studies, crude R^2 did not differ by recording period, body position, wear time or accelerometer output type, and was not correlated with population's mean age. Further, in both groups crude R^2 was invers correlated with sample size, but without statistical significance at the 5% level (*AEE studies*: $r_{Spearman} = -0.37$, p=0.13; *AEE per kg studies*: $r_{Spearman} = -0.51$, p=0.07).

[15] In the framework of this thesis, this figure has already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.
[16] In the framework of this thesis, parts of the results on "Sensitivity analysis considering AEE as absolute or relative measure" have already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

5.2 ActivE study

5.2.1 Recruitment of ActivE study population

According to the target sampling plan (described in paragraph 4.2.1 and **Figure 4-1**), men and women were successfully recruited in each BMI group and age group. The final numbers of recruited participants are presented in **Table 5-4**. It turned out difficult to recruit men in the lowest and women in the highest age group; thus, men of age 60 – 69 and women of age 20 – 29 were slightly overrepresented.

Table 5-4 Number of ActivE study participants stratified by sex, BMI, and age group

	Men (n=25)				Women (n=25)			
Age group	Total	BMI 18.5 – 24.9	BMI 25.0 – 29.9	BMI ≥ 30.0	Total	BMI 18.5 – 24.9	BMI 25.0 – 29.9	BMI ≥ 30.0
20 – 29 years	2	2	-	-	8	4	3	1
30 – 39 years	5	2	2	1	5	3	2	-
40 – 49 years	6	1	4	1	5	2	2	1
50 – 59 years	4	1	2	1	5	2	1	2
60 – 69 years	8	3	4	1	2	-	2	-
Total	25	9	12	4	25	11	10	4

This table refers to the recruitment scheme described in Figure 4-1 and paragraph 4.2.1

5.2.2 Characteristics of ActivE study population

In this paragraph the ActivE study population is described in detail. Presented characteristics were chosen with regard to relevance for prediction analyses.

Anthropometric and socio-economic characteristics of the participating men and women are provided in **Table 5-5**. Due to the recruitment issues mentioned above, men were slightly older than women. Both men and women were stable in weight during the 2-weeks examination period, which is important for the energy expenditure analyses. The majority of participants was full-time employed (56 % of men and women), and had a high level of school education (72 % of men, 84 % of women), and a high level of professional qualification (68 % of men, 72 % of women). Most of the examinations (68 %) took place in autumn and winter (21th of September to 20th of March).

Table 5-5 Characteristics of ActivE study population regarding anthropometry, socio-economy, season of examination

	Men (n=25)			Women (n=25)		
	Mean	**± SD**	**(Min – Max)**	**Mean**	**± SD**	**(Min – Max)**
Age [years]	49.9	± 13.8	(26.0 – 69.0)	40.0	± 14.6	(20.0 – 68.0)
Height T1 [cm]	181.0	± 6.0	(172.1 – 194.1)	167.5	± 6.5	(156.8 – 183.6)
Difference height T1-T2 [cm]	-0.05	± 0.30	(-0.70 – 0.70)	-0.01	± 0.31	(-0.70 – 0.50)
Weight T1 [kg]	87.8	± 12.1	(67.0 – 120.1)	72.5	± 12.7	(52.4 – 97.2)
Difference weight T1-T2 [kg]	0.22	± 0.99	(-2.00 – 2.45)	0.13	± 0.93	(-2.00 – 1.85)
BMI [kg/m²]	26.8	± 3.5	(21.1 – 36.1)	25.9	± 4.6	(18.6 – 35.4)
Waist circumference T1 [cm]	95.8	± 9.9	(79.0 – 115.1)	84.3	± 12.0	(68.8 – 113.1)
Hip circumference T1 [cm]	103.4	± 5.4	(92.6 – 117.3)	104.2	± 8.1	(90.5 – 124.2)
Waist-Hip-Ratio T1 [cm]	0.93	± 0.07	(0.81 – 1.07)	0.81	± 0.07	(0.72 – 1.00)
	N	**(%)**		**N**	**(%)**	
Occupation						
Full-time employed	14	(56 %)		14	(56 %)	
Part-time employed[a]	2	(8 %)		8	(32 %)	
Not employed	9	(36 %)		3	(12 %)	
School education						
No qualification for university/ college entrance	7	(28 %)		4	(16 %)	
Qualification for university/ college entrance	18	(72 %)		21	(84 %)	
Professional qualification						
Completed vocational/ educational training	8	(32 %)		7	(28 %)	
Completed academical training	9	(36 %)		10	(40 %)	
Completed both trainings	8	(32 %)		8	(32 %)	
Season of examination						
Spring	5	(20 %)		6	(24 %)	
Summer	3	(12 %)		2	(8 %)	
Autumn	9	(36 %)		9	(36 %)	
Winter	8	(32 %)		8	(32 %)	

Data are presented as mean, standard deviation (SD), minimum (Min) and maximum (Max), or absolute (N) and relative numbers (%) for men and women. T1 and T2 refer to measurements of the first or second study center visit. [a] part-time employed includes also the categories semi-retirement, marginally/ irregularly/ occasionally employed.

Characteristics of body composition, handgrip strength and blood pressure are provided in **Table 5-6**. With both measurement methods (BIA and ADP) absolute and relative FFM was higher in men than in women, for relative FM vice versa. Maximum handgrip strength was higher in men than in women. Men had slightly higher blood pressure and lower resting heart rate compared to women. (Measurements of systolic and diastolic blood pressure were not corrected for medication treatment [231], which would be indicated in 4 male participants who took antihypertensive treatment).

Table 5-6 Characteristics of ActivE study population regarding body composition (BIA, ADP), handgrip strength and blood pressure

	Men (n=25)			Women (n=25)		
	Mean	**± SD**	**(Min – Max)**	**Mean**	**± SD**	**(Min – Max)**
FM_{BIA} [kg]	23.3	± 8.3	(6.3 – 45.4)	25.9	± 9.7	(12.8 – 47.5)
$FM\%_{BIA}$ [%]	25.9	± 6.5	(9.3 – 37.8)	34.8	± 8.0	(24.4 – 48.9)
FFM_{BIA} [kg]	64.6	± 6.1	(53.5 – 79.7)	46.6	± 6.0	(36.7 – 58.4)
$FFM\%_{BIA}$ [%]	74.1	± 6.5	(62.2 – 90.7)	65.2	± 8.0	(51.1 – 75.6)
FM_{ADP} [kg]	23.8	± 10.2	(4.5 – 49.2)	26.3	± 11.7	(9.3 – 52.1)
$FM\%_{ADP}$ [%]	26.3	± 8.3	(6.7 – 41.4)	35.0	± 10.8	(16.0 – 53.8)
FFM_{ADP} [kg]	64.0	± 5.1	(53.6 – 72.2)	46.2	± 6.2	(34.3 – 60.5)
$FFM\%_{ADP}$ [%]	73.7	± 8.3	(58.6 – 93.3)	65.0	± 10.8	(46.2 – 84.0)
Handgrip strength, maximum [kg]	49.0	± 7.1	(36.7 – 68.2)	31.5	± 7.3	(18.5 – 44.6)
Systolic blood pressure [mmHg]	126.6	± 10.4	(110.5 – 149.5)	117.4	± 15.2	(99.0 – 157.5)
Diastolic blood pressure [mmHg]	78.9	± 6.3	(69.0 – 93.5)	74.2	± 9.8	(57.5 – 96.0)
Resting heart rate [beats/min]	60.9	± 8.8	(43.5 – 80.5)	66.6	± 9.2	(52.0 – 85.0)

Data are presented as mean, standard deviation (SD), minimum (Min) and maximum (Max) for men and women. ADP air-displacement plethysmography, BIA bioelectrical impedance analysis, FFM fat-free mass, FM fat mass.

Characteristics regarding alcohol consumption, smoking, and energy and macronutrient intake are provided in **Table 5-7**. The majority of the women (64 %) and one half of the men (48 %) consumed alcohol once per week or less, whereas the other half of men (52 %) consumed alcohol more than once per week. This was reflected by the absolute daily alcohol intake that was higher in men than in women. Further, the majority of participants was never or former smokers (72 % of men, 80 % of women). Male current smokers had more pack-years than female, whereas female former smokers had more pack-years than male.

Daily energy intake was higher in men than in women, and was mostly attributed to carbohydrate intake for both sexes. The absolute intake of carbohydrates did not differ statistically between men and women, whereas the absolute intake of fat and protein was higher in men than in women. The relative intake of carbohydrates, fat and protein was similar between men and women.

Table 5-7 Characteristics of ActivE study population regarding alcohol consumption, smoking, energy and macronutrient intake, and resting respiratory quotient

	Men (n=25)			Women (n=25)		
	N	**(%)**		**N**	**(%)**	
Alcohol consumption, frequency						
1x per week or less	12	(48 %)		16	(64 %)	
More than 1x per week	13	(52 %)		9	(36 %)	
Smoking status						
Never smoker	9	(36 %)		12	(48 %)	
Current smoker	7	(28 %)		5	(20 %)	
Former smoker	9	(36 %)		8	(32 %)	
	Median		**($P25^{th}$, $P75^{th}$)**	**Median**		**($P25^{th}$, $P75^{th}$)**
Pack years of smoking	0.39		(0.00, 7.00)	0.14		(0.00, 7.00)
Pack years of smoking (excl. never smoker)	5.25		(0.41, 16.38)	7.00		(0.75, 10.00)
Pack years of smoking (only current smoker)	2.55		(0.39, 17.00)	0.43		(0.27, 4.25)
Pack years of smoking (only former smoker)	7.00		(1.57, 15.75)	8.50		(4.25, 24.50)
Alcohol intake [g/d]	17.0		(11.3, 26.9)	8.0		(0.4, 16.0)
	Mean	**± SD**	**(Min – Max)**	**Mean**	**± SD**	**(Min – Max)**
Energy intake [kcal/d]	2450	± 516	(1580 – 3890)	1957	± 496	(1190 – 3000)
Carbohydrate intake [g/d]	262	± 72	(136 – 477)	227	± 66	(130 – 391)
Carbohydrate intake, relative [%]	43.5	± 7.1	(27.0 – 52.0)	47.2	± 6.9	(31.0 – 57.0)
Fat intake [g/d]	94	± 27	(57 – 166)	71	± 26	(30 – 130)
Fat intake, relative [%]	33.6	± 4.8	(27.0 – 49.0)	31.7	± 6.0	(19.0 – 44.0)
Protein intake [g/d]	99	± 22	(64 – 153)	77	± 23	(36 – 126)
Protein intake, relative [%]	16.6	± 2.5	(12.0 – 22.0)	16.2	± 3.2	(11.0 – 26.0)
Fasting RQ in resting phase	0.85	± 0.04	(0.77 – 0.91)	0.82	± 0.04	(0.74 – 0.92)

Data are presented as mean, standard deviation (SD), minimum (Min) and maximum (Max), or median, 25^{th} and 75^{th} percentile ($P25^{th}$, $P75^{th}$), or absolute (N) and relative numbers (%) for men and women. RQ respiratory quotient

Physical activity (PA) parameters derived from questionnaires are provided in **Table 5-8**. The questionnaire of physical activity of previous 12 months (QUAP) examined PA within various domains of daily life during the last year. The International Physical Activity Questionnaire (IPAQ, short version) examined PA of the previous seven days and is more focused on PA intensity. Both questionnaires collected information about time spent sitting and sleeping, but the design of asking was different. There were no differences for any parameter between men and women.

Table 5-8 Characteristics of ActivE study population regarding physical activity information based on questionnaires (QUAP, IPAQ)

	Men (n=25)			Women (n=25)		
QUAP	**Median**		**(P25th, P75th)**	**Median**		**(P25th, P75th)**
Time in occupation [h/week]	38.0		(0.0, 40.5)	39.0		(14.0, 40.0)
Time in locomotion [h/week]	2.5		(1.1, 4.5)	4.8		(1.8, 7.0)
Time in domestic work and gardening [h/week]	7.0		(5.0, 15.0)	10.0		(4.0, 15.0)
Time in leisure time bicycling [h/week]	0.6		(0.1, 1.4)	0.6		(0.1, 1.3)
Time in leisure time walking [h/week]	0.5		(0.2, 1.4)	1.0		(0.6, 1.4)
Time in sports/exercise [h/week]	2.7		(1.5, 5.5)	2.0		(1.2, 4.2)
Total time in locomotion, bicycling, walking, sports [h/week]	7.3		(5.3, 9.2)	11.2		(6.9, 14.4)
Total time in locomotion, bicycling, walking, sports, domestic work [h/week]	13.5		(10.5, 27.3)	21.5		(16.4, 27.7)
Total time in occupation, locomotion, bicycling, walking, sports, domestic work [h/week]	49.4		(36.3, 57.3)	53.4		(36.5, 62.1)
	Mean	**± SD**	**(Min – Max)**	**Mean**	**± SD**	**(Min – Max)**
Time spent sitting [h/d]	9.4	± 3.1	(2.6 – 14.0)	10.5	± 3.0	(3.7 – 16.1)
Time spent sleeping excl. napping [h/d]	7.0	± 0.7	(5.5 – 8.0)	7.3	± 0.9	(5.5 – 9.0)
Time spent sleeping incl. napping [h/d]	7.2	± 0.7	(6.0 – 8.5)	7.5	± 1.1	(5.5 – 11.0)
IPAQ-Short	**Median**		**(P25th, P75th)**	**Median**		**(P25th, P75th)**
Time in vigorous PA [min/d]	25.7		(8.6, 42.9)	17.1		(4.3, 34.3)
Time in moderate PA [min/d]	5.7		(0.0, 25.7)	6.4		(0.0, 25.7)
Time in walking activity [min/d]	19.3		(4.3, 30.0)	17.1		(8.6, 60.0)
Total time in moderate PA, walking activity [min/d]	30.0		(8.6, 50.0)	41.4		(17.1, 98.6)
Total time in vigorous PA, moderate PA, walking activity [min/d]	53.6		(42.9, 82.9)	57.7		(37.1, 128.6)
	Mean	**± SD**	**(Min – Max)**	**Mean**	**± SD**	**(Min – Max)**
Time spent sleeping incl. napping [h/d]	7.3	± 1.0	(5.0 – 10.0)	7.1	± 1.0	(5.0 – 10.0)
Time spent sitting [h/d]	7.9	± 3.3	(2.5 – 14.0)	6.9	± 3.8	(1.5 – 15.0)

Data are presented as mean, standard deviation (SD), minimum (Min) and maximum (Max), or median, 25th and 75th percentile (P25th, P75th) for men and women. IPAQ International Physical Activity Questionnaire, PA physical activity, QUAP questionnaire of physical activity of previous 12 months.

Regarding medical history, at the time of examination no participants had ever been diagnosed with diabetes mellitus, stroke/apoplexy, cardiac insufficiency/heart failure, or myocardial infarction. The frequency of diagnoses of diseases is listed in **Table 5-9**. Of those eight men diagnosed with increased cholesterol/triglycerides, one man was treated in the last 12 months, of those four men diagnosed with hypertension all men were treated in the past 12 months. Of those six women diagnosed with thyroid disease, two women have been treated in the last 12 months.

Table 5-9 Characteristics of ActivE study population regarding frequency of ever diagnosed diseases

	Men (n=25)		Women (n=25)	
	N	(%)	N	(%)
Diabetes mellitus	0		0	
Increased cholesterol/triglycerides	8	(32 %)	2	(8 %)
Hypertension	4	(16 %)	1	(4 %)
Thyroid disease	1	(4 %)	6	(24 %)
Myocardial infarction	0		0	
Cardiovascular disease/angina pectoris	1	(4 %)	0	
Cardiac arrhythmia	1	(4 %)	0	
Cardiac insufficiency/heart failure	0		0	
Stroke/apoplexy	0		0	
Cancer	1	(4 %)	0	

Data are presented as absolute (N) and relative numbers (%) of men and women who ever had been diagnosed with the disease by a physician.

The measurement results of total energy expenditure (TEE) and its components are shown in **Table 5-10**. Men had higher TEE (ca. 600 kcal/d), higher resting energy expenditure (REE, ca. 300 kcal/d), and higher activity-related energy expenditure (AEE, ca. 200 kcal/d) compared to women. The average proportion of REE and of AEE related to TEE were similar in men and women. Further, it should be noticed, that the ranges of AEE (ca. 1120 kcal/d in men, ca. 1440 kcal/d in women) and TEE (ca. 1400 kcal/d in men, ca. 1890 kcal/d in women) were obviously wide.

Table 5-10 Characteristics of ActivE study population regarding total energy expenditure and its components

	Men (n=25)			Women (n=25)		
	Mean	± SD	(Min – Max)	Mean	± SD	(Min – Max)
TEE, measured by DLW [kcal/d]	3158	± 408	(2496 – 3905)	2571	± 464	(1813 – 3704)
DIT [kcal/d, 10% of TEE]	316	± 41	(250 – 391)	257	± 46	(181 – 370)
REE, measured by IC [kcal/d]	1832	± 195	(1444 – 2280)	1517	± 142	(1287 – 1869)
REE [% of TEE]	58.5	± 6.8	(48.4 – 77.1)	60.1	± 8.1	(43.4 – 82.2)
AEE [kcal/d]	1010	± 301	(321 – 1446)	797	± 338	(152 – 1595)
AEE [% of TEE]	31.5	± 6.8	(12.9 – 41.6)	29.9	± 8.1	(7.8 – 46.6)

Data are presented as mean, standard deviation (SD), minimum (Min) and maximum (Max) for men and women. AEE was calculated as TEE – REE – 0.1*TEE. AEE activity-related energy expenditure, DIT diet-induced thermogenesis, DLW doubly-labeled water, IC indirect calorimetry, REE resting energy expenditure, TEE total energy expenditure.

Concentration of blood parameters of lipid and glucose metabolism and inflammation, which were measured in blood samples collected after overnight fasting, are provided in **Table 5-11**. HDL-cholesterol was higher in women and cholesterol-HDL-ratio was lower in women compared to men. Two participants had a noticeably high CRP concentration (25.1 mg/l and 13.0 mg/l), which was considered in sensitivity analyses.

Table 5-11 Characteristics of ActivE study population regarding concentration of blood parameters of lipid and glucose metabolism and inflammation after overnight fasting

	Men (n=25)			**Women (n=25)**		
	Mean	**± SD**	**(Min – Max)**	**Mean**	**± SD**	**(Min – Max)**
Cholesterol [mmol/l]	5.67	± 1.08	(3.50 – 7.70)	5.48	± 1.14	(3.90 – 7.60)
HDL-cholesterol [mmol/l]	1.38	± 0.33	(0.90 – 2.20)	1.57	± 0.28	(1.20 – 2.20)
LDL-cholesterol [mmol/l][a]	3.90	± 0.82	(2.21 – 5.48)	3.56	± 0.87	(2.30 – 5.18)
Cholesterol-HDL-ratio	4.25	± 1.01	(2.90 – 6.20)	3.61	± 1.00	(2.30 – 6.20)
Glucose [mmol/l]	5.49	± 0.48	(4.60 – 6.50)	5.16	± 0.80	(4.00 – 7.30)
HbA_{1c} [%]	5.26	± 0.27	(4.90 – 5.80)	5.26	± 0.37	(4.30 – 6.20)
C-peptide [ng/ml]	2.05	± 0.70	(1.18 – 3.73)	1.98	± 0.76	(0.96 – 3.60)
	Median		**($P25^{th}$, $P75^{th}$)**	**Median**		**($P25^{th}$, $P75^{th}$)**
Triglycerides [mmol/l]	1.30		(1.00, 1.50)	1.00		(0.70, 1.20)
Insulin [mU/l]	6.10		(4.50, 9.70)	5.70		(3.50, 8.50)
HOMA index	1.49		(1.13, 2.50)	1.60		(0.68, 1.93)
CRP [mg/l]	1.30		(1.00, 2.50)	1.20		(0.40, 2.80)

Data are presented as mean, standard deviation (SD), minimum (Min) and maximum (Max), or median, 25th and 75th percentile (P25th, P75th) for men and women. [a] LDL concentration was directly measured except for two participants; for them LDL concentration based on calculated values.

5.2.3 **Physical activity parameter based on accelerometry data**

Non-wear-time analysis conducted in ActiLife resulted in the exclusion of one complete day from calculation of accelerometer-derived PA parameters in one participant (Appendix **Table 10-2**). Calculated PA parameters derived from accelerometry are presented in **Table 5-12**. The overall activity parameters (i.e. *VM counts per minute, Axis 1 counts per minute, Axis 2 counts per minute, Axis 3 counts per minute, steps per day*) and the intensity-specific parameters were similar in men and women. Combining men and women, participants spent on average 130 ± 34 minutes per day in PA with low intensity (range 71 – 242 min/d), 98 ± 24 minutes per day in PA with moderate intensity (range 53 – 164 min/d), and 21 ± 11 minutes per day in PA with vigorous intensity (range 6 – 51 min/d). *Time in total activity* amounted to 250 ± 58 minutes per day (147 – 398 min/d), of which a proportion of 52.2 ± 5.6 % was spent in low PA, a proportion of 39.5 ± 5.2 % was spent in moderate PA, and a proportion of 8.3 ± 3.6 % was spent in vigorous PA.

Table 5-12 Characteristics of ActivE study population regarding physical activity parameters derived from accelerometry

	Men (n=25)			Women (n=25)		
	Mean	**± SD**	**(Min – Max)**	**Mean**	**± SD**	**(Min – Max)**
Vector magnitude counts [cpm]	439	± 126	(258 – 711)	458	± 119	(269 – 721)
Axis 1 counts [cpm]	230	± 82	(121 – 394)	247	± 87	(126 – 428)
Axis 2 counts [cpm]	244	± 79	(143 – 448)	280	± 69	(186 – 437)
Axis 3 counts [cpm]	272	± 70	(153 – 436)	253	± 70	(121 – 443)
Steps per day	8297	± 2613	(4709 – 14517)	9256	± 3095	(5438 – 17869)
Steps per minute	5.76	± 1.82	(3.27 – 10.09)	6.43	± 2.15	(3.77 – 12.41)
Time in inactivity [min/d]	1199	± 63	(1061 – 1293)	1181	± 53	(1042 – 1278)
Time in low PA [min/d]	122	± 33	(71 – 196)	138	± 33	(83 – 242)
Time in moderate PA [min/d]	97	± 28	(53 – 164)	100	± 21	(61 – 143)
Time in vigorous PA [min/d]	22	± 11	(6 – 45)	21	± 12	(6 – 51)
Time in MVPA [min/d]	119	± 34	(67 – 198)	120	± 28	(70 – 172)
Time in total activity [min/d]	241	± 63	(147 – 379)	259	± 53	(162 – 398)
Proportion of time in low PA [%]	50.9	± 5.5	(39.9 – 62.6)	53.4	± 5.5	(41.4 – 63.7)
Proportion of time in moderate PA [%]	40.3	± 5.7	(29.7 – 54.1)	38.8	± 4.7	(28.9 – 48.8)
Proportion of time in vigorous PA [%]	8.9	± 3.5	(3.7 – 15.1)	7.8	± 3.7	(2.6 – 18.6)

Data are presented as mean, standard deviation (SD), minimum (Min) and maximum (Max) for men and women. Axis 1 (Y), 2 (X) and 3 (Z) refers to collected data of acceleration in vertical, horizontal front-back and horizontal left-right direction [232]. Intensity of physical activity was defined as inactive (0 – 78 cpm), low (79 – 2689 cpm), moderate (2690 – 6166 cpm), vigorous (≥6167 cpm) based on *VM counts per minute* [139]. cpm counts per minute, MVPA moderate-to-vigorous physical activity, PA physical activity.

Spearman rank correlation analysis between all accelerometer-derived activity parameters revealed that the overall activity parameters (i.e. *VM counts per minute, Axis 1 counts per minute, Axis 2 counts per minute, Axis 3 counts per minute, steps per day*) were strongly associated with each other (range of $r_{Spearman}$: 0.654 – 0.922), as well as with *time in total activity* (range of $r_{Spearman}$: 0.791 – 0.916), and with the absolute *time in low PA, moderate PA* and *vigorous PA* (range of $r_{Spearman}$: 0.546 – 0.874) (Appendix **Table 10-5**) Further, each of the overall activity parameters was inversely correlated with *proportion in low PA* (range of $r_{Spearman}$: -0.378 – -0.290), and positive correlated with *proportion in vigorous PA* (range of $r_{Spearman}$: 0.336 – 0.613), but not with *proportion in moderate PA* (Appendix **Table 10-5**).

Absolute *time spent in low PA, moderate PA* and *vigorous PA* was positively correlated with each other (range of $r_{Spearman}$: 0.318 – 0.594), and each with *time in total activity* (range of $r_{Spearman}$: 0.568 – 0.884). But there was no correlation between *time in total activity* and the *proportions in low, moderate and vigorous PA*, as well as between *proportion in moderate PA* and *proportion in vigorous PA*. Whereas, the *proportion in low PA* was invers correlated with *proportion in moderate PA* ($r_{Spearman}$: -0.766) and *proportion in vigorous PA* ($r_{Spearman}$: -0.464) (Appendix **Table 10-5**).

5.3 Prediction of AEE based on physical activity derived from accelerometry data

For all analyses regarding development of prediction models for DLW-derived AEE and corresponding association analyses, one participant was excluded due to abnormal thyroid hormone levels in the blood indicating a thyroid dysfunction. Thus, the analytical sample size for this analysis part was reduced to 49 observations.

Of initial >200 potential variables, 76 variables remained for prediction model development after initial screening for redundant variables and variables with missing values. These remaining variables were grouped with regard to context or examination module as listed in **Table 5-14**. Accelerometer-derived parameters were regarded separately.

5.3.1 (Crude) Association of accelerometer-derived parameters with AEE

A linear regression analysis was conducted to examine the association of accelerometer-derived parameters and AEE, and to find out which parameter is appropriate for AEE prediction. Thirteen accelerometer-derived parameters were taken into account. The parameters *Axis 1 counts* and *VM counts* explained 34.0 % and 33.8 % of the variance in AEE (Model 1 and 2 in **Table 5-13**), which was the highest proportion within the single parameters, closely followed by the parameters *Steps per minute* (32.5 % explained variance in AEE, Model 6) and *Steps per day* (32.4 % explained variance in AEE, Model 5).

The parameters *time in low PA*, *time in moderate PA* and *time in vigorous PA* explained only 20.9 – 26.5 % of the variance in AEE when included separately (Models 7, 8, 9); but when all three parameters were included in one model, 36.1 % of the variance in AEE was explained (Model 14).

The parameter *time in total activity* (which is actually the sum of time in low, moderate and vigorous PA) explained 31.2 % of the variance in AEE. Whereas the single parameters *proportion in low PA*, *proportion in moderate PA* and *proportion in vigorous PA* explained only a small amount of the variance in AEE (0.1 – 8.1 %, Models 11, 12, 13). But including the three parameters *time in total activity* and *proportion in moderate* and *proportion in vigorous PA* together in one model, 35.3 % of the variance in AEE was explained (Model 15).

For AEE prediction model development, both *VM counts* and *Axis 1 counts* were used, because the proportion of explained variance in AEE was similarly high. Further, *VM counts* was an often used accelerometer output variable in other studies where triaxial accelerometers were applied (Appendix **Table 10-4**) [233]. The main-selection step was conducted separately for both parameters.

Table 5-13 Association of single accelerometer parameters (crude models) and multiple parameters with AEE [kcal/d] using linear regression models (n=49)

Model	Variable	beta	SE	p-value	STbeta	VIF	R^2	adj.R^2
Single parameter models (crude)								
1	Intercept	183.23	152.27	0.235	0.00		0.338	0.323
	VM counts [cpm]	1.60	0.33	<0.001	0.58			
2	Intercept	348.07	119.40	0.005	0.00		0.340	0.326
	Axis 1 counts [cpm]	2.32	0.47	<0.001	0.58			
3	Intercept	347.08	154.00	0.029	0.00		0.231	0.214
	Axis 2 counts [cpm]	2.12	0.56	0.000	0.48			
4	Intercept	231.26	162.80	0.162	0.00		0.279	0.264
	Axis 3 counts [cpm]	2.55	0.60	0.000	0.53			
5	Intercept	321.89	128.64	0.016	0.00		0.324	0.310
	Steps per day	0.07	0.01	0.000	0.57			
6	Intercept	321.57	128.53	0.016	0.00		0.325	0.311
	Steps per minute	95.50	20.07	0.000	0.57			
7	Intercept	305.90	174.73	0.087	0.00		0.209	0.192
	Time in low PA [min/d]	4.56	1.29	0.001	0.46			
8	Intercept	277.84	179.45	0.128	0.00		0.215	0.198
	Time in moderate PA [min/d]	6.34	1.77	0.001	0.46			
9	Intercept	579.80	88.90	<0.001	0.00		0.265	0.249
	Time in vigorous PA [min/d]	15.20	3.69	<0.001	0.51			
10	Intercept	97.14	178.97	0.590	0.00		0.312	0.298
	Time in total activity [min/d]	3.21	0.70	<0.001	0.56			
11	Intercept	1398.30	452.15	0.003	0.00		0.025	0.004
	Proportion in low PA [%]	-9.49	8.61	0.276	-0.16			
12	Intercept	974.98	373.88	0.012	0.00		0.001	-0.020
	Proportion in moderate PA [%]	-1.84	9.39	0.846	-0.03			
13	Intercept	684.29	116.67	<0.001	0.00		0.081	0.062
	Proportion in vigorous PA [%]	26.29	12.88	0.047	0.29			
Multiple parameter models (mutually adjusted)								
14	Intercept	162.04	181.85	0.378	0.00	0.000	0.361	0.318
	Time in low PA [min/d]	1.81	1.53	0.243	0.18	1.652		
	Time in moderate PA [min/d]	2.89	2.08	0.170	0.21	1.623		
	Time in vigorous PA [min/d]	10.31	4.00	0.013	0.35	1.288		
15	Intercept	-265.03	400.40	0.511	0.00	0.000	0.353	0.309
	Time in total activity [min/d]	3.06	0.71	<0.001	0.53	1.053		
	Proportion in moderate PA [%]	6.21	7.99	0.441	0.10	1.070		
	Proportion in vigorous PA [%]	18.61	11.53	0.114	0.20	1.090		

Beta (unstandardized regression coefficient) = mean difference in AEE [kcal/d] per unit difference of variable. STbeta (standardized regression coefficient) = mean difference in AEE per SD difference of variable. R^2 (coefficient of determination) = explained variance of the model. adj. adjusted, cpm counts per minute, PA physical activity, SE standard error, VIF variance inflation factor, VM vector magnitude.

Additionally, to improve interpretability, two more sets of accelerometer parameters were investigated. Set 1 contained the parameters *time in low PA, time in moderate PA, time in vigorous PA*; set 2 contained the parameters *time in total activity, proportion in moderate PA, proportion in vigorous PA*. The main-selection step was conducted separately for each set, which was forced to be included in the model as one group.

5.3.2 **Variable groups and preselection step**

Beside the accelerometer-derived parameters, the other variables were assigned to 16 groups (**Table 5-14**). The 'Nutrition' module was considered creating two separate groups, because of the dependence of energy intake on the intake of carbohydrates, fat and protein. In each group significant variables for AEE prediction were selected by stepwise selection regression. Finally, 11 variables were selected during this preselection step and were used in the subsequent main selection step.

Table 5-14 Variable groups and its candidate variables of which significant variables for AEE prediction were selected using stepwise selection regression (n=49)

Variable Group	Candidate variables for preselection step	
	Not selected (not significant)	**Selected (significant)**
ADP	FM_{ADP}, $FM\%_{ADP}$	**FFM_{ADP}**
BIA	FM_{BIA}, $FM\%_{BIA}$	**FFM_{BIA}**
Anthropometry	weight, BMI, waist circumference, hip circumference, WHR, arm circumference	**height**
QUAP	time in occupation; MET-h in occupation; time in domestic work; MET-h in domestic work; time in bicycling; MET-h in bicycling; time in walking; time in sports; total time in locomotion, bicycling, walking, sports; total time in locomotion, bicycling, walking, sports, domestic work; total time in occupation, locomotion, bicycling, walking, sports, domestic work	**time in locomotion**
IPAQ	time in vigorous PA, time in moderate PA, time in walking activity, total time in moderate and vigorous PA, total time in moderate and vigorous PA and walking activity	**total time in moderate PA and walking activity**
Sitting (from QUAP & IPAQ)	*IPAQ*: time spent sitting; *QUAP*: time spent sitting on weekdays, time spent sitting on weekend	**time spent sitting (QUAP)**
Sleeping (from QUAP & IPAQ)	*IPAQ*: time spent sleeping (incl. napping); *QUAP*: time spent sleeping (incl. napping), time spent sleeping (excl. napping)	--
Nutrition set 1	fat intake, relative fat intake, relative carbohydrate intake, protein intake, relative protein intake	**carbohydrate intake**
Nutrition set 2	fat intake, relative fat intake, carbohydrate intake, relative carbohydrate intake, protein intake, relative protein intake	**energy intake**
Blood pressure	systolic blood pressure, diastolic blood pressure	**resting heart rate**
Physical fitness		**handgrip strength**
Demography	age	**sex**
Metabolism	fasting respiratory quotient	--
Socioeconomic	school education, professional qualification, occupation	--
Lifestyle	smoking status, pack years of smoking, frequency of alcohol consumption, alcohol intake	--
Other	season of examination	--

In each group all candidate variables were offered to select significant variables for AEE prediction by stepwise selection regression using p-value limits of 0.05 for the corresponding partial F-statistic for including and retaining variables in the model. Variables of the accelerometry group were regarded separately (**Table 5-13**). ADP air-displacement plethysmography, BIA bioelectrical impedance analysis, FFM fat-free mass, FM fat mass, IPAQ International Physical Activity Questionnaire, MET metabolic equivalent of task, PA physical activity, QUAP questionnaire of physical activity of previous 12 months, WHR waist-to-hip ratio.

5.3.3 **Association between preselected variables and AEE**

To assess the crude association of each preselected variable with AEE a single linear regression was conducted. The results are presented in **Table 5-15** with preselected variables and accelerometer-derived variables sorted in descending order by strength of association given by the standardized regression coefficient (STbeta, equivalent to Pearson correlation coefficient) or the coefficient of determination (R^2).

The accelerometer-derived parameters *Axis 1 counts* and *VM counts* were equally strong associated with AEE, closely followed by *fat-free mass by ADP*. *Time spent sitting* (from QUAP), *resting heart rate* and *sex* (being female) were inversely associated with AEE; all the remaining variables were positively associated with AEE. Each variable was significant at the 5% level to the corresponding t-test.

Looking at the residuals, there were no apparent deviations from normal distribution or homogenous variance distribution in the residuals, hence no transformation of variables was necessary.

Table 5-15 Crude association of significant preselected variables and accelerometer-derived parameters with AEE [kcal/d] using single linear regression (n=49)

Preselected variables	beta	SE	95% CI	p-value	STbeta	R^2
Axis 1 counts [cpm]	2.32	0.47	(1.37, 3.27)	<0.001	0.58	0.340
VM counts [cpm]	1.60	0.33	(0.94, 2.26)	<0.001	0.58	0.338
FFM_{ADP} [kg]	18.48	3.87	(10.69, 26.27)	<0.001	0.57	0.326
FFM_{BIA} [kg]	15.29	3.96	(7.33, 23.25)	<0.001	0.49	0.241
Height [cm]	18.07	4.71	(8.60, 27.53)	<0.001	0.49	0.239
Energy intake [kcal/d]	0.29	0.08	(0.14, 0.45)	<0.001	0.48	0.232
Carbohydrate intake [g/d]	2.08	0.62	(0.83, 3.33)	0.002	0.44	0.193
$Sitting_{QUAP}$ [h/d]	-46.30	14.27	(-75.00, -17.60)	0.002	-0.43	0.183
HGS_{max} [kg]	11.85	3.95	(3.90, 19.81)	0.004	0.40	0.160
Resting heart rate [bpm]	-13.96	5.11	(-24.24, -3.69)	0.009	-0.37	0.137
$Locomotion_{QUAP}$ [h/week]	21.40	8.78	(3.74, 39.06)	0.019	0.34	0.112
Sex (male=0, female=1)	-220.05	92.14	(-405.41, -34.69)	0.021	-0.33	0.108
$MPA+walking_{IPAQ}$ [min/d]	2.25	1.11	(0.01, 4.49)	0.049	0.28	0.080

Variables are sorted in descending order by strength of association with AEE. Beta (unstandardized regression coefficient) = mean difference in AEE [kcal/d] per unit difference of variable. STbeta (standardized regression coefficient) = mean difference in AEE per SD difference of variable. R^2 (coefficient of determination) = explained variance of the model. ADP air-displacement plethysmography, BIA bioelectrical impedance analysis, bpm beats per minute, cpm counts per minute, FFM fat-free mass, HGS handgrip strength, IPAQ International Physical Activity Questionnaire, MPA moderate physical activity, QUAP questionnaire of physical activity of previous 12 months, SE standard error, VM vector magnitude.

Spearman rank correlation analysis revealed that AEE was moderately to strongly correlated with all preselected variables (range of $r_{Spearman}$: 0.329 – 0.609), with an inverse correlation for *time spent sitting, resting heart rate* and *sex* (Appendix **Table 10-6**). The anthropometric variables (i.e. *height,* FFM_{BIA}*,* FFM_{ADP}) were strongly correlated with one another (range of $r_{Spearman}$: 0.857 – 0.955), and with *handgrip strength* (range of $r_{Spearman}$: 0.768 – 0.812). *Energy intake* was strongly correlated with *carbohydrate intake* ($r_{Spearman}$: 0.789). The accelerometer-derived activity parameters *Axis 1 counts* and *VM counts* were strongly correlated with each other ($r_{Spearman}$: 0.924). The questionnaire-derived activity parameters (i.e. *time in locomotion, time spent sitting*, and *time in moderate PA and walking*) were weakly or not correlated with one another or with other preselected variables (Appendix **Table 10-6**).

In ANOVA analysis, *sex* was strongly correlated with *height, fat-free mass by ADP, fat-free mass by BIA, handgrip strength*, and *energy intake*. In sex-adjusted partial Spearman rank correlation analysis, the above mentioned associations were weaker in some cases, but remained statistically significant at the 5% level (Appendix **Table 10-7**).

5.3.4 **Two-parameter models for AEE prediction**

To determine how much variance of AEE can be explained by one accelerometer-derived parameter and one additional significant parameter two-parameter models were calculated using linear regression. The results of the two-parameter models using *VM counts (per minute)* as accelerometer-derived parameter are presented in **Table 5-16**, the two-parameter models using *Axis 1 counts (per minute)* as accelerometer-derived parameter are presented in **Table 5-17**.

As second predictors, anthropometric variables (*fat-free mass by ADP, fat-free mass by BIA, height*) added the highest proportion of explained variance in AEE ranging between 19.2 – 26.7 % in both VM counts and Axis 1 counts models; thus the total explained variance ranged between 53.3 – 60.5 % in these models. A considerable proportion of explained variance in AEE of about 15 % was added by *handgrip strength* and *sex*, and about 9 – 12 % was added by *energy intake* and *carbohydrate intake* as second predictors. The questionnaire-derived activity parameters *time in locomotion* and *time in moderate PA and walking* added the lowest proportion of explained variance in AEE (0.7 – 3.1 %), and lost statistical significance when added as second predictors.

Table 5-16 Linear regression models on AEE [kcal/d] using accelerometer-derived *VM counts* and each significant preselected variable (n=49)

Model	Variable	beta	SE	p-value	STbeta	pR²	VIF	R²	adj.R²
1	Intercept	-685.55	195.88	0.001	0.00	.	0.000	0.605	0.588
	VM counts [cpm]	1.46	0.26	<0.001	0.53	0.338	1.010		
	FFM_{ADP} [kg]	16.81	3.01	<0.001	0.52	0.267	1.010		
2	Intercept	-686.73	206.45	0.002	0.00	.	0.000	0.584	0.566
	VM counts [cpm]	1.61	0.26	<0.001	0.59	0.338	1.000		
	FFM_{BIA} [kg]	15.46	2.96	<0.001	0.50	0.247	1.000		
3	Intercept	-2672.31	652.01	<0.001	0.00	.	0.000	0.538	0.518
	VM counts [cpm]	1.51	0.28	<0.001	0.55	0.338	1.005		
	Height [cm]	16.60	3.72	<0.001	0.45	0.200	1.005		
4	Intercept	-192.76	180.56	0.291	0.00	.	0.000	0.462	0.438
	VM counts [cpm]	1.36	0.31	<0.001	0.49	0.338	1.061		
	Energy intake [kcal/d]	0.22	0.07	0.002	0.36	0.124	1.061		
5	Intercept	-131.02	174.26	0.456	0.00	.	0.000	0.449	0.425
	VM counts [cpm]	1.42	0.31	<0.001	0.52	0.338	1.039		
	Carbohydrate intake [g/d]	1.61	0.53	0.004	0.34	0.111	1.039		
6	Intercept	592.55	220.92	0.010	0.00	.	0.000	0.414	0.389
	VM counts [cpm]	1.38	0.32	<0.001	0.50	0.338	1.084		
	$Sitting_{QUAP}$ [h/d]	-31.19	12.72	0.018	-0.29	0.077	1.084		
7	Intercept	-272.82	183.03	0.143	0.00	.	0.000	0.489	0.467
	VM counts [cpm]	1.58	0.29	<0.001	0.57	0.338	1.000		
	HGS_{max} [kg]	11.52	3.12	0.001	0.39	0.152	1.000		
8	Intercept	875.09	340.38	0.013	0.00	.	0.000	0.403	0.377
	VM counts [cpm]	1.45	0.32	<0.001	0.53	0.338	1.044		
	Resting heart rate [bpm]	-9.87	4.39	0.029	-0.26	0.066	1.044		
9	Intercept	205.51	154.53	0.190	0.00	.	0.000	0.349	0.321
	VM counts [cpm]	1.47	0.36	<0.001	0.53	0.338	1.199		
	$Locomotion_{QUAP}$ [h/week]	7.53	8.32	0.370	0.12	0.012	1.199		
10	Intercept	523.63	164.99	0.003	0.00	.	0.000	0.485	0.463
	VM counts [cpm]	1.70	0.29	<0.001	0.62	0.338	1.009		
	Sex (male=0, female=1)	-257.90	71.08	0.001	-0.39	0.147	1.009		
11	Intercept	172.45	151.79	0.262	0.00	.	0.000	0.358	0.330
	VM counts [cpm]	1.50	0.34	<0.001	0.54	0.338	1.066		
	$MPA+walking_{IPAQ}$ [min/d]	1.17	0.97	0.233	0.15	0.020	1.066		

Two-parameter models containing *VM counts* as accelerometer-derived parameter and one of the 11 preselected variables, which turned out significant in the stepwise selection of each variable group (**Table 5-14**). Adj. adjusted, ADP air-displacement plethysmography, beta unstandardized regression coefficient, BIA bioelectrical impedance analysis, bpm beats per minute, cpm counts per minute, FFM fat-free mass, HGS handgrip strength, IPAQ International Physical Activity Questionnaire, MPA moderate physical activity, QUAP questionnaire of physical activity of previous 12 months, SE standard error, STbeta standardized regression coefficient, pR² partial explained variance of the variable, VIF variance inflation factor, R² explained variance of the model, VM vector magnitude.

Table 5-17 Linear regression models on AEE [kcal/d] using accelerometer-derived *Axis 1 counts* and each significant preselected variable (n=49)

Model	Variable	beta	SE	p-value	STbeta	pR^2	VIF	R^2	adj.R^2
1	Intercept	-518.94	184.02	0.007	0.00	.	0.000	0.601	0.583
	Axis 1 counts [cpm]	2.10	0.37	<0.001	0.53	0.340	1.012		
	FFM_{ADP} [kg]	16.61	3.03	<0.001	0.51	0.261	1.012		
2	Intercept	-520.07	191.33	0.009	0.00	.	0.000	0.587	0.569
	Axis 1 counts [cpm]	2.34	0.38	<0.001	0.59	0.340	1.000		
	FFM_{BIA} [kg]	15.46	2.95	<0.001	0.50	0.246	1.000		
3	Intercept	-2455.87	652.23	<0.001	0.00	.	0.000	0.533	0.512
	Axis 1 counts [cpm]	2.17	0.40	<0.001	0.54	0.340	1.008		
	Height [cm]	16.28	3.74	<0.001	0.44	0.192	1.008		
4	Intercept	2.94	164.02	0.986	0.00	.	0.000	0.440	0.416
	Axis 1 counts [cpm]	1.91	0.46	<0.001	0.48	0.340	1.107		
	Energy intake [kcal/d]	0.20	0.07	0.006	0.33	0.100	1.107		
5	Intercept	65.76	154.28	0.672	0.00	.	0.000	0.429	0.404
	Axis 1 counts [cpm]	2.00	0.46	<0.001	0.50	0.340	1.073		
	Carbohydrate intake [g/d]	1.46	0.55	0.010	0.31	0.088	1.073		
6	Intercept	729.19	195.99	0.001	0.00	.	0.000	0.413	0.388
	Axis 1 counts [cpm]	2.00	0.47	<0.001	0.50	0.340	1.092		
	$Sitting_{QUAP}$ [h/d]	-30.52	12.78	0.021	-0.28	0.073	1.092		
7	Intercept	-106.59	162.84	0.516	0.00	.	0.000	0.490	0.468
	Axis 1 counts [cpm]	2.29	0.42	<0.001	0.57	0.340	1.001		
	HGS_{max} [kg]	11.47	3.12	0.001	0.39	0.150	1.001		
8	Intercept	981.25	330.81	0.005	0.00	.	0.000	0.395	0.369
	Axis 1 counts [cpm]	2.09	0.47	<0.001	0.52	0.340	1.064		
	Resting heart rate [bpm]	-9.11	4.46	0.047	-0.24	0.055	1.064		
9	Intercept	358.18	120.88	0.005	0.00	.	0.000	0.347	0.319
	Axis 1 counts [cpm]	2.16	0.53	<0.001	0.54	0.340	1.246		
	$Locomotion_{QUAP}$ [h/week]	6.03	8.49	0.482	0.09	0.007	1.246		
10	Intercept	701.93	141.77	<0.001	0.00	.	0.000	0.494	0.472
	Axis 1 counts [cpm]	2.49	0.42	<0.001	0.62	0.340	1.011		
	Sex (male=0, female=1)	-264.02	70.53	0.001	-0.39	0.154	1.011		
11	Intercept	311.26	120.26	0.013	0.00	.	0.000	0.372	0.344
	Axis 1 counts [cpm]	2.19	0.47	<0.001	0.55	0.340	1.036		
	$MPA+walking_{IPAQ}$ [min/d]	1.44	0.95	0.136	0.18	0.031	1.036		

Two-parameter models containing *Axis 1 counts* as accelerometer-derived parameter and one of the 11 preselected variables, which turned out significant in the stepwise selection of each variable group (**Table 5-14**). Adj. adjusted, ADP air-displacement plethysmography, beta unstandardized regression coefficient, BIA bioelectrical impedance analysis, bpm beats per minute, cpm counts per minute, FFM fat-free mass, HGS handgrip strength, IPAQ International Physical Activity Questionnaire, MPA moderate physical activity, QUAP questionnaire of physical activity of previous 12 months, SE standard error, STbeta standardized regression coefficient, pR^2 partial explained variance of the variable, VIF variance inflation factor, R^2 explained variance of the model.

5.3.5 **Results of main-selection – final AEE prediction models**

The main-selection step was conducted separately for the accelerometer-derived variables *VM counts*, *Axis 1 counts* and the two accelerometer variable sets: (1) *time in low PA, time in moderate PA, time in vigorous PA* and (2) *time in total activity, proportion in moderate PA, proportion in vigorous PA*.

The final AEE prediction models based on *VM counts* and *Axis 1 counts* are presented in this paragraph (**Table 5-18, Table 5-19**), and in more detail in the Appendix (**Table 10-8, Table 10-9**). The final models based on accelerometer variable set 1 and set 2 are presented in the Appendix (**Table 10-10, Table 10-11**).

5.3.5.1 Selected predictor variables – in general and for specific variable sets

In general, in VM counts and Axis 1 counts models, the accelerometer output variable was always included as first predictor in the model (Appendix **Table 10-8, Table 10-9**). In accelerometer set 1 and set 2 models, the accelerometer variables were forced to be included in the model as the first predictors; however some accelerometer variables were not significant at the 5% level (Appendix **Table 10-10, Table 10-11**).

Further, in all models *fat-free mass by ADP* (if available) was always included as second variable after the accelerometer output variable(s). If no ADP was available, then *fat-free mass by BIA* was included instead. If no ADP or BIA was available (i.e. no measurement of body composition at all), then *height* from anthropometry measurement was included instead (**Table 5-18, Table 5-19**, Appendix **Table 10-8, Table 10-9, Table 10-10, Table 10-11**).

The inclusion of the other potential predictors was less straightforward and depended on the set of variables offered. Regarding additional information from PA questionnaires, if information from IPAQ was available, then *time in moderate PA and walking* was always included in the models.

If information from QUAP was available, then in some models *time spent sitting* and *time in locomotion* were included. In VM counts models, the variables *time spent sitting* and *time in locomotion* were always included together (in five out of nine selected models); in Axis 1 counts models, in two selected models (out of nine) both *time spent sitting* and *time in locomotion* were included, and in three other models only *time spent sitting* was included.

If information from both IPAQ and QUAP was available, then in three selected VM counts models (out of seven) variables from both IPAQ and QUAP were included in the model; in Axis 1 counts models, only in one selected model (out of five) variables from both IPAQ and QUAP were included.

If no information from QUAP was available, then only *time in moderate PA and walking* (from IPAQ) was included. If, in contrast, no information from IPAQ was available, then *time spent sitting* and/or *time in locomotion* (from QUAP) were included instead (if available). If no additional information about QUAP or IPAQ was available at all, then no other predictor variable was included instead (**Table 5-18, Table 5-19**, Appendix **Table 10-8, Table 10-9, Table 10-10, Table 10-11**).

Regarding nutrition-related variables, only *carbohydrate intake* was selected as predictor, while *energy intake* was not. In VM counts models, *carbohydrate intake* was included in ten selected models (out of 11), if information about nutrition was available; in Axis 1 models, *carbohydrate intake* was included in seven selected models (out of 11). If no information of nutrition was available no other variable was included instead (**Table 5-18, Table 5-19,** Appendix **Table 10-8, Table 10-9, Table 10-10, Table 10-11**).

Resting heart rate was included only in three selected VM counts models (out of 20) and in two selected Axis 1 models (out of 19), and was mostly the last included predictor (**Table 5-18, Table 5-19,** Appendix **Table 10-8, Table 10-9, Table 10-10, Table 10-11**). The preselected variables *sex*, *handgrip strength*, and *energy intake* were never included in any final AEE prediction model.

Comparing Model A of VM counts and Axis 1 counts models of the same variable set, in ten settings (out of 15) the same predictors were selected. In five variable settings, VM counts models included 1 – 2 more additional predictors compared to Axis 1 counts models (variables *time in locomotion* and *time spent sitting* in setting 'No ADP & BIA'; variables *time in locomotion* and *carbohydrate intake* in setting 'No IPAQ'; variable *carbohydrate intake* in setting 'No IPAQ & QUAP & ADP' and in setting 'No IPAQ & QUAP & ADP & BIA'; variable *time in locomotion* in setting 'No nutrition & IPAQ').

5.3.5.2 Explained variance (R^2) of AEE

Across all variable settings, in VM counts models 53.8 – 75.4 % (adjusted 51.8 – 71.9 %) of the variance in AEE was explained with 2 – 6 included predictors; in Axis 1 counts models 53.3 – 71.7 % (adjusted 51.2 – 68.4 %) of the variance in AEE was explained with 2 – 5 included predictors (**Table 5-18, Table 5-19,** Appendix **Table 10-8, Table 10-9**).

In models of accelerometer variable set 1 57.3 – 74.1 % (adjusted 53.4 – 70.4 %) of the variance in AEE was explained with 4 – 8 included predictors; in models of accelerometer

variable set 2 55.8 – 73.6 % (adjusted 51.8 – 69.9 %) of the variance in AEE was explained with 4 – 8 included predictors (Appendix **Table 10-10, Table 10-11**).

5.3.5.3 Contribution of single predictors to the explained variance of AEE – Partial R²

In all VM counts models, the accelerometer variable *VM counts (per minute)* explained most of the variance in AEE (partial R^2: *VM counts [cpm]* = 33.8 %). Similarly, in all Axis 1 models, the accelerometer variable *Axis 1 counts (per minute)* explained most of the variance in AEE (partial R^2: *Axis 1 counts [cpm]* = 34.0 %). The second most contributing predictor was one of the three anthropometry variables, depending on which variable was available and therefore included, either *fat-free mass measured by ADP* (partial R^2: FFM_{ADP} = 26.7/26.1 % in VM counts/Axis 1 counts models), or *fat-free mass measured by* BIA (if no ADP was available; partial R^2: FFM_{BIA} = 24.7/24.6 %), or *height* (if no ADP or BIA was available; partial R^2: *height* = 20.0/19.2 %). The other predictors contributed an additional but smaller proportion to the explained variance in AEE, if they were selected (range of partial R^2 in VM counts and Axis 1 counts models: *time in moderate PA and walking* = 4.7 – 9.7 %, *time in locomotion* = 2.4 – 4.4 %, *time spent sitting* = 2.3 – 3.7 %, *carbohydrate intake* = 2.7 – 4.7 %, *resting heart rate* = 2.5 – 4.8 %) (**Table 5-18, Table 5-19,** Appendix **Table 10-8, Table 10-9**).

Comparing predictor-specific regression coefficients across the different variable settings and also between VM counts models and Axis 1 counts models, the regression coefficient values were of similar magnitude. Comparing the regression coefficients values of each predictor variable in the crude analysis (**Table 5-15**) and in the final AEE prediction models (**Table 5-18, Table 5-19**), the regression coefficients values went slightly towards the null or were even similar. Further, the variables *time spent sitting* and *resting heart rate* were still inverse associated with AEE, and all the remaining variables were still positively associated.

Table 5-18 AEE prediction models derived from stepwise selection regression using accelerometer variable VM counts and full or reduced variable sets (n=49)

AEE prediction models	Selected predictor variables Unstandardized Beta (Standard Error), Partial R^2, *p-value*									Model fit	
										R^2	adj.R^2
Variable sets	**VM counts** [cpm]	**FFM_{ADP}** [kg]	**FFM_{BIA}** [kg]	**Height** [cm]	**MPA+walking** $_{IPAQ}$ [min/d]	**Locomotion** $_{QUAP}$ [h/week]	**Sitting** $_{QUAP}$ [h/d]	**Carbohydrate intake** [g/d]	**Resting heart rate** [bpm]	[%]	[%]
Full variable set - Model A	1.16 (0.24) 33.8 % *<0.001*	16.46 (2.84) 26.7 % *<0.001*			2.22 (0.69) 6.4 % *0.002*			1.00 (0.42) 3.9 % *0.020*		70.7	68.1
Full variable set - Model B	0.85 (0.25) 33.8 % *0.001*	15.05 (2.73) 26.7 % *<0.001*			1.55 (0.69) 6.4 % *0.029*	11.56 (5.69) 2.4 % *0.048*	-21.63 (9.18) 2.3% *0.023*	1.15 (0.39) 3.9 % *0.006*		75.4	71.9
no ADP - Model A	1.18 (0.24) 33.8 % *<0.001*		13.83 (2.65) 24.7 % *<0.001*		2.39 (0.70) 5.6 % *0.001*			1.00 (0.42) 4.7 % *0.021*	-7.24 (3.45) 2.9 % *0.042*	71.7	68.4
no ADP - Model B	0.97 (0.26) 33.8 % *<0.001*		13.44 (2.58) 24.7 % *<0.001*		1.29 (0.69) 5.6 % *0.070*	12.08 (5.82) 2.6 % *0.044*	-23.64 (9.33) 2.9 % *0.015*	1.33 (0.40) 4.7 % *0.002*		74.3	70.6
no ADP & BIA - Model A	0.83 (0.27) 33.8 % *0.003*			15.81 (3.33) 20.0 % *<0.001*	1.73 (0.74) 7.9 % *0.024*	12.90 (6.02) 3.0 % *0.038*	-24.17 (9.66) 3.0 % *0.016*	1.25 (0.42) 4.7 % *0.004*		72.4	68.5
no QUAP - Model A	1.16 (0.24) 33.8 % *<0.001*	16.46 (2.84) 26.7 % *<0.001*			2.22 (0.69) 6.4 % *0.002*			1.00 (0.42) 3.9 % *0.020*		70.7	68.1
no IPAQ - Model A	0.90 (0.26) 33.8 % *0.001*	13.72 (2.79) 26.7 % *<0.001*				15.08 (5.73) 4.4 % *0.012*	-27.15 (9.27) 3.7 % *0.005*	1.14 (0.41) 3.8 % *0.008*		72.4	69.2
no IPAQ & QUAP - Model A	1.46 (0.26) 33.8 % *<0.001*	16.81 (3.01) 26.7 % *<0.001*								60.5	58.8
no IPAQ & QUAP - Model B	1.37 (0.25) 33.8 % *<0.001*	14.87 (3.08) 26.7 % *<0.001*						0.91 (0.46) 3.2 % *0.052*		63.7	61.3
no IPAQ & QUAP & ADP - Model A	1.49 (0.25) 33.8 % *<0.001*		13.73 (2.91) 24.7 % *<0.001*					1.08 (0.45) 4.7 % *0.021*		63.1	60.7
no IPAQ & QUAP & ADP & BIA - Model A	1.41 (0.27) 33.8 % *<0.001*			14.14 (3.76) 20.0 % *<0.001*				1.05 (0.49) 4.2 % *0.038*		58.0	55.2

Table 5-18 *Continued*

AEE prediction models	Selected predictor variables Unstandardized Beta (Standard Error), Partial R^2, *p-value*									Model fit	
	VM counts	**FFM_{ADP}**	**FFM_{BIA}**	**Height**	**MPA+walking**	**Locomotion**	**Sitting**	**Carbohydrate**	**Resting heart**	R^2	adj.R^2
Variable sets	[cpm]	[kg]	[kg]	[cm]	$_{IPAQ}$ [min/d]	$_{QUAP}$ [h/week]	$_{QUAP}$ [h/d]	**intake** [g/d]	**rate** [bpm]	[%]	[%]
no Nutrition	1.26 (0.25)	18.50 (2.85)			2.12 (0.72)					66.9	64.6
- Model A	33.8 %	26.7 %			6.4 %						
	<0.001	*<0.001*			*0.005*						
no Nutrition	1.14 (0.25)	16.85 (2.90)			2.49 (0.73)				-6.78 (3.55)	69.4	66.6
- Model B	33.8 %	26.7 %			6.4 %				2.5 %		
	<0.001	*<0.001*			*0.001*				*0.062*		
no Nutrition	1.26 (0.25)	18.50 (2.85)			2.12 (0.72)					66.9	64.6
& QUAP	33.8 %	26.7 %			6.4 %						
- Model A	*<0.001*	*<0.001*			*0.005*						
no Nutrition	1.14 (0.25)	16.85 (2.90)			2.49 (0.73)				-6.78 (3.55)	69.4	66.6
& QUAP	33.8 %	26.7 %			6.4 %				2.5 %		
- Model B	*<0.001*	*<0.001*			*0.001*				*0.062*		
no Nutrition	1.06 (0.27)	16.16 (2.84)				12.89 (6.09)	-24.82 (9.90)			67.5	64.6
& IPAQ	33.8 %	26.7 %				3.3 %	3.7 %				
- Model A	*<0.001*	*<0.001*				*0.040*	*0.016*				
no Nutrition	1.46 (0.26)	16.81 (3.01)								60.5	58.8
& IPAQ & QUAP	33.8 %	26.7 %									
- Model A	*<0.001*	*<0.001*									
no Nutrition	1.61 (0.26)		15.46 (2.96)							58.4	56.6
& IPAQ & QUAP	33.8 %		24.7 %								
& ADP - Model A	*<0.001*		*<0.001*								
no Nutrition & IPAQ	1.51 (0.28)			16.60 (3.72)						53.8	51.8
& QUAP & ADP	33.8 %			20.0 %							
& BIA - Model A	*<0.001*			*<0.001*							
no Nutrition	1.27 (0.25)		15.06 (2.74)		2.35 (0.74)				-9.09 (3.54)	67.9	65.0
& QUAP & ADP	33.8 %		24.7 %		4.7 %				4.8 %		
- Model A	*<0.001*		*<0.001*		*0.003*				*0.014*		

In Model A predictors were selected stepwise if p-value <0.05. Model B (if applicable) yielded a lower SBC during a step of the stepwise selection process.
More details in Appendix **Table 10-8**.

Table 5-19 AEE prediction models derived from stepwise selection regression using accelerometer variable Axis 1 counts and full or reduced variable sets (n=49)

AEE prediction models	Selected predictor variables Unstandardized Beta (Standard Error), Partial R^2, *p-value*									Model fit	
										R^2	adj.R^2
Variable sets	**Axis 1 counts** [cpm]	**FFM_{ADP}** [kg]	**FFM_{BIA}** [kg]	**Height** [cm]	**MPA+walking** $_{IPAQ}$ [min/d]	**Locomotion** $_{QUAP}$ [h/week]	**Sitting** $_{QUAP}$ [h/d]	**Carbohydrate intake** [g/d]	**Resting heart rate** [bpm]	[%]	[%]
Full variable set - Model A	1.68 (0.34) 34.0 % *<0.001*	16.74 (2.83) 26.1 % *<0.001*			2.43 (0.67) 8.0 % *0.001*			0.86 (0.42) 2.8 % *0.048*		70.8	68.1
no ADP - Model A	1.73 (0.35) 34.0 % *<0.001*		14.19 (2.66) 24.6 % *<0.001*		2.59 (0.69) 6.3 % *0.001*			0.86 (0.42) 2.7 % *0.049*	-7.04 (3.45) 4.1 % *0.048*	71.7	68.4
no ADP & BIA - Model A	1.69 (0.37) 34.0 % *<0.001*			17.52 (3.52) 19.2 % *<0.001*	2.70 (0.74) 9.7 % *0.001*			0.96 (0.45) 3.5 % *0.038*		66.5	63.4
no ADP & BIA - Model B	1.52 (0.37) 34.0 % *<0.001*			16.20 (3.49) 19.2 % *<0.001*	2.36 (0.74) 9.7 % *0.003*		-18.92 (10.00) 2.6 % *0.065*	1.02 (0.44) 3.5 % *0.024*		69.0	65.4
no QUAP - Model A	1.68 (0.34) 34.0 % *<0.001*	16.74 (2.83) 26.1 % *<0.001*			2.43 (0.67) 8.0 % *0.001*			0.86 (0.42) 2.8 % *0.048*		70.8	68.1
no IPAQ - Model A	1.88 (0.37) 34.0 % *<0.001*	15.60 (2.96) 26.1 % *<0.001*					-21.70 (10.30) 3.6 % *0.041*			63.7	61.2
no IPAQ - Model B	1.19 (0.41) 34.0 % *0.006*	13.83 (2.88) 26.1 % *<0.001*				15.06 (6.12) 2.8 % *0.018*	-27.61 (9.68) 3.6 % *0.007*	1.06 (0.44) 4.0 % *0.019*		70.5	67.1
no IPAQ & QUAP - Model A	2.10 (0.37) 34.0 % *<0.001*	16.61 (3.03) 26.1 % *<0.001*								60.1	58.3
no IPAQ & QUAP & ADP - Model A	2.34 (0.38) 34.0 % *<0.001*		15.46 (2.95) 24.6 % *<0.001*							58.7	56.9
no IPAQ & QUAP & ADP - Model B	2.14 (0.38) 34.0 % *<0.001*		14.01 (2.96) 24.6 % *<0.001*					0.90 (0.47) 3.2 % *0.060*		61.8	59.3
no IPAQ & QUAP & ADP & BIA - Model A	2.17 (0.40) 34.0 % *<0.001*			16.28 (3.74) 19.2 % *<0.001*						53.3	51.2

Table 5-19 *Continued*

AEE prediction models	Selected predictor variables Unstandardized Beta (Standard Error), Partial R^2, *p-value*									Model fit	
										R^2	adj.R^2
Variable sets	**Axis 1 counts** [cpm]	**FFM_{ADP}** [kg]	**FFM_{BIA}** [kg]	**Height** [cm]	**MPA+walking** $_{IPAQ}$ [min/d]	**Locomotion** $_{QUAP}$ [h/week]	**Sitting** $_{QUAP}$ [h/d]	**Carbohydrate intake** [g/d]	**Resting heart rate** [bpm]	[%]	[%]
no Nutrition	1.86 (0.35)	18.44 (2.80)			2.33 (0.70)					68.0	65.9
- Model A	34.0 %	26.1 %			8.0 %						
	<0.001	*<0.001*			*0.002*						
no Nutrition	1.86 (0.35)	18.44 (2.80)			2.33 (0.70)					68.0	65.9
& QUAP	34.0 %	26.1 %			8.0 %						
- Model A	*<0.001*	*<0.001*			*0.002*						
no Nutrition	1.88 (0.37)	15.60 (2.96)					-21.70 (10.30)			63.7	61.2
& IPAQ	34.0 %	26.1 %					3.6 %				
- Model A	*<0.001*	*<0.001*					*0.041*				
no Nutrition	1.50 (0.41)	16.03 (2.89)				12.19 (6.33)	-24.65 (10.12)			66.5	63.4
& IPAQ	34.0 %	26.1 %				2.8 %	3.6 %				
- Model B	*0.001*	*<0.001*				*0.061*	*0.019*				
no Nutrition	2.10 (0.37)	16.61 (3.03)								60.1	58.3
& IPAQ & QUAP	34.0 %	26.1 %									
- Model A	*<0.001*	*<0.001*									
no Nutrition & IPAQ	2.34 (0.38)		15.46 (2.95)							58.7	56.9
& QUAP & ADP	34.0 %		24.6 %								
- Model A	*<0.001*		*<0.001*								
no Nutrition & IPAQ	2.17 (0.40)			16.28 (3.74)						53.3	51.2
& QUAP & ADP	34.0 %			19.2 %							
& BIA - Model A	*<0.001*			*<0.001*							
no Nutrition	1.88 (0.36)		15.27 (2.69)		2.54 (0.72)				-8.46 (3.50)	69.0	66.2
& QUAP & ADP	34.0 %		24.6 %		6.3 %				4.1 %		
- Model A	*<0.001*		*<0.001*		*0.001*				*0.020*		

In Model A predictors were selected stepwise if p-value <0.05. Model B (if applicable) yielded a lower SBC during a step of the stepwise selection process.
More details in Appendix **Table 10-9**.

5.3.5.4 Regression diagnostics and sensitivity analyses

All final AEE prediction models met the assumptions of normally distributed residuals and homoscedasticity, and no substantial multicollinearity among the predictor variables was detected considering the variance inflation factor (VIF) of the predictor variables and the condition number (CN) of the model.

In sensitivity analyses, after excluding individually influential observations in VM counts and Axis 1 counts models, predictor variables' regression coefficients were similar compared to models with full sample size (Appendix **Table 10-12**, **Table 10-13**). For most predictors the absolute difference of regression coefficients was lower than 1 standard error (<1 SE).
However, in seven models the selected predictor variables lost significance at the 5% level after exclusion of influential observations (*resting heart rate* in four models/variable settings, *carbohydrate intake* in two models/variable settings, and *moderate PA and walking* (from IPAQ) in one model/variable setting). On the other hand, in two models the selected predictor variables reached significance at the 5% level after exclusion of influential observations (*time spent sitting* in Axis 1 counts model 'No ADP & BIA', Model B; and *time in locomotion* in Axis 1 counts model 'No nutrition & IPAQ', Model B).

When AEE prediction models were recalculated selecting variables with forward selection, exactly the same predictors were selected compared to stepwise selection regression for both VM counts models and Axis 1 counts models in each variable setting (Appendix **Table 10-14**).

When AEE prediction models were recalculated selecting variables with backward elimination, except for two VM counts models (variable setting: 'Full variable set', 'No ADP') and one Axis 1 counts model (variable setting: 'No IPAQ') the same predictors were selected compared to stepwise selection regression in each variable setting (Appendix **Table 10-15**). The deviating VM counts model of the 'Full variable set' additionally selected the variables *time in locomotion* and *time spent sitting*; thus this model is equivalent to Model B of the 'Full variable set' (**Table 5-18**). The deviating VM counts model of the 'No ADP' variable set additionally selected the variables *time in locomotion* and *time spent sitting*, while the variables *time in moderate PA and walking* and *resting heart rate* were not selected; thus this model would be a new variant.
The deviating Axis 1 counts model of the 'No IPAQ' variable set additionally selected the variables *time in locomotion* and *carbohydrate intake*; thus this model is equivalent to Model B of variable set 'No IPAQ' (**Table 5-19**).

When AEE prediction models were recalculated selecting variables with LASSO and optimized SBC criterion, in nearly every model 1 – 4 additional predictors were selected compared to stepwise selection regression models (*resting heart rate* in 11 VM counts models and eight Axis 1 counts models; *time in locomotion* in three VM counts models and six Axis 1 counts models; *time spent sitting* in three VM counts models and four Axis 1 counts models; *carbohydrate intake* in one VM counts model and four Axis 1 counts models, *height* in three VM counts models and two Axis 1 counts models) (Appendix **Table 10-16**).
Some predictors were first-time selected: *handgrip strength* in three VM counts models and two Axis 1 counts models; *sex* in two VM counts models; *energy intake* in one VM counts model.

When AEE prediction model development was replicated in 2000 bootstrap samples using stepwise selection and LASSO selection with optimized SBC criterion, the bootstrap inclusion frequencies of the selected variables reflected the results obtained from the original data analysis for both VM counts models and Axis 1 counts models (Appendix **Table 10-17, Table 10-18**). Basically, bootstrap inclusion frequencies were higher for LASSO selection compared to stepwise selection. Across all variable settings, the accelerometer-derived variables *VM counts* and *Axis 1 counts* were selected in 82.6 – 99.6 % (stepwise selection, Appendix **Table 10-17**) or in 98.5 – 100 % (LASSO selection, Appendix **Table 10-18**) of the bootstrap models.
Depending on which anthropometric method was available, *fat-free mass by ADP* was selected in 76.3 – 87.0 % (stepwise selection) or in 81.2 – 94.1 % (LASSO selection) of the bootstrap models, *fat-free mass by BIA* (if no ADP was available) was selected in 71.2 – 83.2 % (stepwise selection) or in 95.5 – 98.1 % (LASSO selection) of the bootstrap models, and *height* (if no ADP and BIA was available) was selected in 64.9 – 77.4 % (stepwise selection) or in 90.0 – 95.9 % (LASSO selection) of the bootstrap models.
Regarding variables derived from PA questionnaire, when stepwise selection was used, only *time in moderate PA and walking* (from IPAQ) had an acceptable high inclusion frequency (43.1 – 82.6 %). When LASSO selection was used, all variables derived from PA questionnaire (overall 55.0 – 97.5 %), and *carbohydrate intake* (58.7 – 84.7 %) obtained acceptable high inclusion frequencies. Depending on the variable setting, *resting heart rate* was included in 26.9 – 87.2 % of the bootstrap models when LASSO selection was used.
The other variables were selected with much lower bootstrap inclusion frequencies and failed to reach the 60 % mark in all variable settings [227].

5.4 Association of duration and intensity of PA with cardiometabolic factors

The association of duration and intensity of PA with factors of inflammation, glucose metabolism and lipid metabolism was investigated using partial Spearman rank correlation (adjusted for sex and age) and linear regression analysis. The descriptive characteristics of cardiometabolic factors (**Table 5-11**) and of activity parameters derived from accelerometry (**Table 5-12**) in the study population were presented above (paragraph 5.2.3).

5.4.1 Partial Spearman rank correlation analysis between accelerometer-derived activity parameters and cardiometabolic factors

Age- and sex-adjusted Spearman rank correlation analysis between accelerometer-derived activity parameters and cardiometabolic factors revealed that absolute *time in moderate PA* ($r_{Spearman}$: -0.358), and *time in total activity* ($r_{Spearman}$: -0.366) were both invers associated with *glucose* concentration; absolute *time in vigorous PA* was positively associated with *HDL-cholesterol* concentration ($r_{Spearman}$: 0.334), and invers associated with *CRP* concentration ($r_{Spearman}$: -0.363), *insulin* concentration ($r_{Spearman}$: -0.312) and *HOMA index* ($r_{Spearman}$: -0.347); relative *proportion in vigorous PA* was positively associated with *HDL-cholesterol* concentration ($r_{Spearman}$: 0.291), and invers associated with *CRP* concentration ($r_{Spearman}$: -0.376) (Appendix **Table 10-19**).

5.4.2 Linear regression analysis of accelerometer-derived PA parameters and cardiometabolic factors

The results of the linear regression analysis when activity parameters were included separately are presented in **Table 5-20**. There was an inverse association of *time in total activity* and *glucose* concentration, *time in moderate PA* and *glucose* concentration, and *time in vigorous PA* and log-*CRP* concentration. No association was found between any factors of lipid metabolism and time in PA of any intensity (**Table 5-20**).

Table 5-20 Association of separate activity parameters and cardiometabolic factors in linear regression models (n=50)

Activity parameter	Time in total activity [30min/d]	Time in low PA [30min/d]	Time in moderate PA [30min/d]	Time in vigorous PA [30min/d]
Cardiometabolic factor	***Mean difference in cardiometabolic factor (95% CI)***			
Cholesterol [mmol/l]	0.06 (-0.10, 0.21)	0.14 (-0.12, 0.41)	-0.02 (-0.37, 0.34)	0.35 (-0.41, 1.10)
HDL-C [mmol/l]	0.02 (-0.02, 0.06)	0.01 (-0.07, 0.08)	0.07 (-0.03, 0.16)	0.08 (-0.13, 0.29)
LDL-C [mmol/l]	0.03 (-0.08, 0.14)	0.09 (-0.11, 0.29)	-0.03 (-0.29, 0.24)	0.25 (-0.31, 0.81)
Log-Triglycerides [mmol/l]	-0.02 (-0.10, 0.05)	0.00 (-0.13, 0.13)	-0.10 (-0.27, 0.07)	-0.15 (-0.52, 0.22)
Cholesterol-HDL -ratio	-0.01 (-0.14, 0.13)	0.08 (-0.16, 0.32)	-0.16 (-0.47, 0.16)	-0.07 (-0.75, 0.62)
Log-CRP [mg/l]	0.02 (-0.13, 0.17)	0.14 (-0.12, 0.40)	0.03 (-0.32, 0.38)	-0.76 (-1.47, -0.06)*
Glucose [mmol/l]	-0.09 (-0.17, -0.01)*	-0.11 (-0.26, 0.04)	-0.24 (-0.43, -0.06)*	-0.28 (-0.70, 0.15)
Log-Insulin [mU/l]	-0.04 (-0.11, 0.02)	-0.05 (-0.17, 0.07)	-0.09 (-0.25, 0.06)	-0.27 (-0.60, 0.05)
HbA_{1c} [%]	-0.00 (-0.05, 0.05)	-0.01 (-0.10, 0.08)	-0.01 (-0.13, 0.10)	0.04 (-0.21, 0.29)
C-peptide [ng/ml]	-0.03 (-0.11, 0.05)	-0.07 (-0.21, 0.07)	-0.03 (-0.22, 0.15)	-0.09 (-0.48, 0.31)
Log-HOMA index	-0.06 (-0.13, 0.00)	-0.08 (-0.20, 0.05)	-0.14 (-0.30, 0.01)	-0.33 (-0.67, 0.01)

All models were adjusted for sex, age, BMI, smoking status, and alcohol consumption.
* p<0.05. PA physical activity.

Taking the interdependence between activity parameters into account, mutually adjusted models were created that include the activity parameters (1) *time in low PA*, *time in moderate PA* and *time in vigorous PA* (mutually adjusted combination A, **Table 5-21**), and (2) *time in total activity*, *proportion in moderate PA* and *proportion in vigorous PA* (mutually adjusted combination B, **Table 5-22**).

Similar to the separate activity parameter models, *time in vigorous PA* was inversely associated with log-*CRP* concentration, which was even stronger in the mutually adjusted model. The association between *time in moderate PA* and *glucose* concentration was of same strength in the mutually adjusted model, but lost significance at the 5% level (**Table 5-21**).

Further, *time in total activity* was inversely associated with *glucose* concentration, which was of similar strength compared to the separate activity parameter model, and *proportion in vigorous PA* (based on time in total activity) was inversely associated with log-*CRP* concentration (**Table 5-22**).

Table 5-21 Association of mutually adjusted activity parameters (combination A) with cardiometabolic factors in linear regression models (n=50)

Activity parameter	Time in low PA [30min/d]	Time in moderate PA [30min/d]	Time in vigorous PA [30min/d]
Cardiometabolic factor	***Mean difference in cardiometabolic factor (95% CI)***		
Cholesterol [mmol/l]	0.21 (-0.14, 0.57)	-0.25 (-0.72, 0.21)	0.31 (-0.55, 1.17)
HDL-C [mmol/l]	-0.04 (-0.14, 0.06)	0.09 (-0.04, 0.22)	0.05 (-0.18, 0.29)
LDL-C [mmol/l]	0.14 (-0.12, 0.40)	-0.19 (-0.54, 0.15)	0.26 (-0.38, 0.90)
Log-Triglycerides [mmol/l]	0.09 (-0.09, 0.26)	-0.15 (-0.37, 0.08)	-0.13 (-0.55, 0.30)
Cholesterol-HDL-ratio	0.26 (-0.06, 0.57)	-0.35 (-0.76, 0.06)	-0.06 (-0.82, 0.70)
Log-CRP [mg/l]	0.32 (-0.00, 0.64)	-0.00 (-0.42, 0.41)	-1.15 (-1.92, -0.38)*
Glucose [mmol/l]	0.01 (-0.18, 0.21)	-0.24 (-0.49, 0.01)	-0.07 (-0.54, 0.39)
Log-Insulin [mU/l]	0.01 (-0.15, 0.17)	-0.06 (-0.26, 0.15)	-0.23 (-0.61, 0.14)
HbA_{1c} [%]	-0.01 (-0.13, 0.11)	-0.02 (-0.18, 0.14)	0.08 (-0.21, 0.37)
C-peptide [ng/ml]	-0.08 (-0.27, 0.11)	0.04 (-0.21, 0.29)	-0.02 (-0.48, 0.44)
Log-HOMA index	0.01 (-0.15, 0.17)	-0.10 (-0.31, 0.11)	-0.25 (-0.64, 0.14)

All models were adjusted for sex, age, BMI, smoking status, and alcohol consumption.
* p<0.05. PA physical activity.

Table 5-22 Association of mutually adjusted activity parameters (combination B) with cardiometabolic factors in linear regression models (n=50)

Activity parameter	Time in total activity [30min/d]	Proportion in moderate PA [% of total]	Proportion in vigorous PA [% of total]
Cardiometabolic factor	***Mean difference in cardiometabolic factor (95% CI)***		
Cholesterol [mmol/l]	0.04 (-0.12, 0.19)	-0.05 (-0.11, 0.01)	0.02 (-0.06, 0.10)
HDL-C [mmol/l]	0.02 (-0.03, 0.06)	0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)
LDL-C [mmol/l]	0.02 (-0.10, 0.13)	-0.03 (-0.08, 0.01)	0.02 (-0.04, 0.08)
Log-Triglycerides [mmol/l]	-0.02 (-0.10, 0.05)	-0.02 (-0.05, 0.01)	-0.02 (-0.06, 0.02)
Cholesterol-HDL-ratio	-0.01 (-0.14, 0.13)	-0.05 (-0.11, 0.00)	-0.03 (-0.10, 0.05)
Log-CRP [mg/l]	0.06 (-0.08, 0.20)	-0.03 (-0.08, 0.03)	-0.11 (-0.19, -0.04)*
Glucose [mmol/l]	-0.10 (-0.18, -0.02)*	-0.03 (-0.06, 0.00)	0.00 (-0.04, 0.05)
Log-Insulin [mU/l]	-0.04 (-0.11, 0.03)	-0.01 (-0.03, 0.02)	-0.02 (-0.06, 0.02)
HbA_{1c} [%]	-0.01 (-0.06, 0.05)	0.00 (-0.02, 0.02)	0.01 (-0.02, 0.04)
C-peptide [ng/ml]	-0.03 (-0.11, 0.05)	0.01 (-0.02, 0.04)	0.00 (-0.04, 0.05)
Log-HOMA index	-0.06 (-0.13, 0.01)	-0.01 (-0.04, 0.01)	-0.02 (-0.06, 0.02)

All models were adjusted for sex, age, BMI, smoking status, and alcohol consumption.
* p<0.05. PA physical activity.

5.4.3 Sensitivity analyses for linear regression of accelerometer-derived PA parameters and cardiometabolic factors

In approach I of sensitivity analysis, one participant taking statins was excluded from calculation of all models for *cholesterol*, *HDL, LDL, cholesterol-HDL-ratio, Log-triglycerides*, and *Log-CRP*. All found associations remained significant. Among the mutually adjusted activity parameter models, additionally, *time in low PA* was associated with *Log-CRP* [beta coefficient (95% CI) = 0.35 (0.03, 0.67) p=0.033], and also with *cholesterol-HDL-ratio* [beta coefficient (95% CI) = 0.31 (0.00, 0.61) p=0.049] (compared to combination A, **Table 5-21**); and *proportion in moderate PA* was associated with *cholesterol-HDL-ratio* [beta coefficient (95% CI) = -0.06 (-0.11, -0.00) p=0.037] (compared to combination B, **Table 5-22**). The remaining results did not change.

In approach II of sensitivity analysis, two participants with elevated CRP levels >10 mg/l [228] (CRP levels were 25.1 and 13.0 mg/l) were excluded from calculation of all models for *Log-CRP*. Additionally, a third participant with a borderline elevated CRP level of 9.8 mg/l was excluded in a separate analysis (all three participants were detected as outliers when CRP levels were depicted as boxplot); and in another separate analysis, one participant taking statins was excluded. All found associations between *time in vigorous PA* or *proportion in vigorous PA* and *Log-CRP* remained significant, but were slightly attenuated in the models of separate and mutually adjusted activity parameters.

The newly occurred association between *time in low PA* and *Log-CRP* (mutually adjusted model, combination A) during approach I of the sensitivity analysis, now became weaker and lost significance again [beta coefficient (95% CI) = 0.24 (-0.04, 0.51) p=0.089], when two participants with CRP levels >10 mg/l and one participant taking statins were excluded.

In approach III of sensitivity analysis, participants detected as influential observations by evaluating diagnostic statistics (studentized residuals, leverages, Cook's distance, Dfbetas of activity parameters) were excluded individually for each regression model (Appendix **Table 10-3**) [217, 220].

The found associations in the separate activity parameter models remained significant, and even became slightly stronger, after excluding influential observations. Additionally, *time in moderate PA* was associated with *HDL concentration* [beta coefficient (95% CI) = 0.10 (0.01, 0.19) p=0.028], after two influential observations were excluded (compared to **Table 5-20**).

Among the mutually adjusted activity parameter models, found association between *time in vigorous PA* or *proportion in vigorous PA* and *Log-CRP* remained significant and changed only

slightly after exclusion of four influential observations. The found association between time in total activity and glucose concentration was attenuated and lost significance [beta coefficient (95% CI) = -0.08 (-0.16, 0.01) p=0.090], when four influential observations were excluded (compared to **Table 5-22**). Additionally, new associations occurred between *time in moderate PA* and *glucose concentration* [beta coefficient (95% CI) = -0.27 (-0.54, -0.01) p=0.041], when two influential observations were excluded (compared to combination A, **Table 5-21**); and between *time in total activity* and *Log-HOMA index* [beta coefficient (95% CI) = -0.07 (-0.13, -0.00) p=0.049], when two influential observations were excluded (compared to combination B, **Table 5-22**).

Considering that exclusion of participants could lower variation that would lead to lower standard deviations and consequently lower p-values, however, when p-values were adjusted for multiple testing no association would be statistically significant.

5.4.4 **Association of AEE with cardiometabolic factors**

The association between AEE and cardiometabolic factors was investigated using linear regression analysis; the results are presented in **Table 5-23**. Three approaches were investigated: (1) including AEE directly measured from DLW method, (2) including predicted AEE that was calculated based on prediction model 'Model A' from variable setting 'full set - VM', (3) including predicted AEE that was calculated based on prediction model 'Model B' from variable setting VM counts & 'full variable set' (Appendix **Table 10-8**, paragraph 5.3.5). 'Model A' was chosen as main model that considered the full set of (preselected) variables, *vector magnitude counts* as activity parameter and a p-value limit of <0.05 for variable selection. 'Model B' was chosen, because it revealed the highest explained variance of AEE among all developed prediction models.

The association between AEE and cardiometabolic factors was calculated for crude AEE (no adjustment) and for AEE adjusted for sex, age, BMI, smoking status and alcohol consumption, analog to the activity parameter models (paragraph 5.4.2). To receive adequate numbers for beta coefficients and confidence intervals, the units of the AEE variables were converted to '1000 kcal/day' (instead of 'kcal/day').

Glucose concentration was inversely correlated with AEE in adjusted models, regardless of whether AEE was measured or predicted. Further, *HOMA index* was inversely correlated with predicted AEE in adjusted models (**Table 5-23**).

Table 5-23 Association of AEE measured by DLW and AEE calculated from prediction models with cardiometabolic factors (n=49)

AEE	AEE_{DLW} [per 1000 kcal/d]		AEE_{pred1} [per 1000 kcal/d]		AEE_{pred2} [per 1000 kcal/d]	
	crude	adjusted	crude	adjusted	crude	adjusted
Cardiometabolic factor	***Mean difference in cardiometabolic factor (95% CI)***					
Cholesterol [mmol/l]	-0.06 (-1.01, 0.90)	0.19 (-0.70, 1.09)	-0.06 (-1.20, 1.08)	0.47 (-0.66, 1.60)	-0.02 (-1.12, 1.09)	0.38 (-0.70, 1.46)
HDL-C [mmol/l]	-0.14 (-0.42, 0.13)	-0.03 (-0.28, 0.21)	-0.11 (-0.44, 0.22)	0.09 (-0.22, 0.39)	-0.08 (-0.40, 0.24)	0.09 (-0.20, 0.39)
LDL-C [mmol/l]	0.16 (-0.59, 0.90)	0.27 (-0.39, 0.94)	0.12 (-0.77, 1.01)	0.39 (-0.45, 1.23)	0.15 (-0.70, 1.01)	0.33 (-0.47, 1.14)
Log-Triglycerides [mmol/l]	-0.04 (-0.47, 0.40)	-0.04 (-0.48, 0.40)	-0.04 (-0.55, 0.48)	-0.01 (-0.57, 0.55)	-0.03 (-0.53, 0.47)	-0.01 (-0.55, 0.52)
Cholesterol-HDL-ratio	0.40 (-0.51, 1.31)	0.31 (-0.49, 1.11)	0.27 (-0.82, 1.36)	0.14 (-0.89, 1.17)	0.21 (-0.85, 1.27)	0.04 (-0.94, 1.02)
Log-CRP [mg/l]	-0.30 (-1.20, 0.61)	-0.38 (-1.26, 0.49)	-0.34 (-1.42, 0.74)	-0.52 (-1.63, 0.59)	-0.25 (-1.30, 0.80)	-0.34 (-1.41, 0.72)
Glucose [mmol/l]	-0.36 (-0.94, 0.22)	-0.50 (-0.99, -0.01)*	-0.61 (-1.29, 0.06)	-0.89 (-1.48, -0.30)*	-0.65 (-1.30, 0.01)	-0.89 (-1.45, -0.34)*
Log-Insulin [mU/l]	-0.02 (-0.53, 0.49)	-0.12 (-0.51, 0.26)	-0.19 (-0.80, 0.41)	-0.41 (-0.88, 0.06)	-0.24 (-0.82, 0.34)	-0.37 (-0.82, 0.08)
HbA_{1c} [%]	0.04 (-0.24, 0.32)	0.09 (-0.21, 0.38)	-0.10 (-0.43, 0.24)	-0.06 (-0.44, 0.32)	-0.03 (-0.36, 0.29)	0.02 (-0.34, 0.38)
C-Peptide [ng/ml]	-0.02 (-0.64, 0.61)	-0.10 (-0.53, 0.33)	-0.17 (-0.92, 0.57)	-0.28 (-0.82, 0.26)	-0.27 (-0.98, 0.45)	-0.31 (-0.83, 0.21)
Log-HOMA index	-0.10 (-0.66, 0.47)	-0.23 (-0.63, 0.17)	-0.31 (-0.98, 0.35)	-0.59 (-1.06, -0.11)*	-0.36 (-1.00, 0.28)	-0.55 (-1.01, -0.10)*

Crude models included only AEE as independent variable. Adjusted models included AEE, sex, age, BMI, smoking status, and alcohol consumption as independent variables. AEE_{DLW} = 'measured' AEE derived from DLW method. AEEpred1 = predicted AEE calculated using Model A from setting VM counts & 'full variable set'. AEEpred2 = predicted AEE calculated using Model B from setting VM counts & 'full variable set' (Appendix **Table 10-8)**.

* p<0.05. AEE activity-related energy expenditure, DLW doubly-labeled water.

6 Discussion

6.1 Systematic review of activity-related energy expenditure predicted by accelerometer-derived physical activity data under free-living conditions[17]

In the present thesis, studies examining the association of accelerometer-derived PA parameters and AEE under free-living conditions were reviewed to investigate (1) to what extent the variance in AEE was explained by accelerometer-derived PA output, (2) to what extent methodological conditions (such as study design, accelerometer device properties, characteristics of the study population) are associated with the explained variance in AEE, and (3) to what extent additional parameters (such as age, sex, body composition) can improve the prediction of AEE.

In 19 identified articles incorporating 28 underlying studies, crude accelerometer outputs explained 4 – 80 % of the variance in DLW-derived AEE. This heterogeneity across the studies was only explained by sample size, getting lower explained variance with larger sample size; whereas other methodological conditions, such as accelerometer output type (uniaxial vs. triaxial) or output metrics (counts vs. steps vs. other), length of recording period ($\leq$ 1 week vs. > 1 week), body placement of the accelerometer (trunk vs. limbs), default wear time (waking hours vs. 24 hours) or age of study population did not systematically explain this heterogeneity. The explained variance in AEE was improved by including additional predictors beyond accelerometer output, independent of the number of additional predictors.

The large heterogeneity in explained variance in AEE might partly be attributed to heterogeneity in the study designs, which could have been reflected in the observed correlation between explained variance in AEE and sample size. Studies with smaller sample sizes tended to explain more variance in AEE by crude accelerometer output. In smaller studies participants often belong to a special or selectively chosen group (for example, conscripts [190] or elderly [90, 181]) that is very similar in regard to individual characteristics such as age, weight, height, body composition or activity patterns. Assuming that these individual characteristics may also affect AEE, then their contribution to explain variance in AEE would be smaller due to small variation within the study population, and consequently, the contribution of accelerometer-derived PA outputs would be larger in studies of small sample size.

[17] In the framework of this thesis, parts of the discussion on "Systematic review of activity-related energy expenditure predicted by accelerometer-derived physical activity data under free-living conditions" have already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

Similarly, the type and range of performed activities might be more identical and less varying in smaller and selective study groups, which could diminish the explained variance in AEE predicted from accelerometer-derived PA outputs compared to studies with more heterogeneous types of activities. Unfortunately, accelerometers cannot provide information about the type of activities, but only information about frequency, duration, and intensity of PA derived from processed acceleration measurements [18, 40, 42, 103]. Thus, without having additional information available from the published studies for example by self-report, a more detailed analysis considering the association of type of activities on the explained variance in AEE was not possible in this review. In addition, depending on the placement at the body accelerometers might detect different types of activity with different accuracy [18, 40]; for example, hip-worn accelerometers may be more likely to detect movements of the trunk, but less likely to detect isolated movements of upper or lower limbs [18, 40, 102]. Although, the placement of the accelerometer on the body could determine whether and how valid the different activities are detected [127], in this review the placement was not associated with the explained variance of AEE.

Furthermore, a large number of accelerometer devices is available, of which 19 different devices from 15 different manufacturers were used in the studies included in this review. As each manufacturer uses proprietary procedures to process the recorded acceleration signals (including filtering, amplifying, sampling, converting, and integration of signals) to provide accelerometer outputs, commonly called activity counts, these outputs are not comparable between different accelerometers and may further have contributed to the heterogeneity across the studies [18, 98, 107, 108, 119, 120]. Unfortunately, it was not possible to investigate whether this existing diversity of accelerometer devices may systematically account for the differences in the explained variances across studies, because neither any information on data processing was readily available from the included publications, nor an aggregated analysis by manufacturer or device model, which might have acted as a proxy for data processing techniques [119, 122], was feasible in view of the great number of different devices and manufacturers.

Furthermore, the daily duration of wear time may affect the variance of AEE explained by accelerometry-assessed PA. In this review, no significant differences were found between studies that record PA for 24 hours vs. waking hours only. However, not only the fact that included studies used different definitions of minimum waking hours to get a valid day, but also that, in general, insufficient recording time ($\leq$12 hours/day) may lead to an

underestimation of PA [234], might have further contributed to the heterogeneity in the results. This illustrates the issue of choosing an appropriate length of recording period that should cover a person's typical activity pattern without having negative impact on compliance [127].

In this review, no significant differences of the explained variance in AEE were found between studies using triaxial accelerometer outputs versus studies using uniaxial outputs. However, it has been suggested that triaxial accelerometers may detect PA with higher validity than uniaxial devices [25, 127, 235], especially activities in sedentary or standing postures [12, 127]. Two included articles that analyzed both the uniaxial and the triaxial output of the same accelerometer found a slightly higher explained variance of AEE for the triaxial output compared to the uniaxial output ($R^2 = 0.81$ vs 0.77 [188]; $R^2 = 0.29$ vs 0.27 [183]). These findings indicate that both types of accelerometer outputs may provide comparable information for AEE prediction in free-living subjects [127].

The extension of the prediction models by adding additional predictors resulted in an increase in the explained variance of AEE, which at 12.5 – 86 % still covered a considerable range. But the total number of predictors in the model did not explain the variance in AEE. Similarly, the number of additional predictors (in addition to accelerometer output) did not explain the improvement of the explained variance in AEE, contributed by the inclusion of the additional predictors. The partial explained variance for accelerometer output ranged from 4 – 41 %. These findings suggest that for a strong AEE prediction model the type of predictor with its underlying information may be more important than the number of predictors. However, because of the arbitrary nature of accelerometer-derived 'activity counts' [18] and the low number of studies in this analysis, comparisons between studies regarding accelerometer output and improvement by additional predictors are limited, and therefore have to be interpreted cautiously.

In this review, body weight and fat-free mass were the most frequently used predictors to improve the explained variance in AEE. Both factors appear to be physiologically plausible, because both are associated with energy expenditure and PA [26]. Interestingly, models that included fat-free mass instead of body weight explained a slightly higher amount of variance in AEE [185-188]. This could be explained by the higher impact of fat-free mass on AEE and PA compared to fat mass or weight [188, 236], because fat-free mass is the metabolic active component of weight [26]. For example, two individuals of same PA and weight may differ in

AEE due to different proportions of fat-free mass and fat mass [26], which demonstrates the difference between AEE and PA. Other factors also related to energy expenditure, such as height, age and sex, were less frequently included in the prediction models.

The strength of this review is that only studies examining the association of accelerometer-derived PA output and performed in free-living conditions using DLW were considered in the analysis. Previous reviews summarized studies comparing accelerometer-derived AEE with DLW-derived AEE, or studies using predefined activity protocols performed under laboratory conditions [23-25, 237], which could mislead the interpretation of association and prediction of AEE by accelerometry in free-living populations.

The main limitations of this review were the small number of identified studies and their substantial heterogeneity in study characteristics. For example, most included studies reported results on AEE used as absolute measure, but some studies reported results only on AEE relative to body weight. Sensitivity analyses revealed that the explained variance in AEE was slightly but not significantly higher in studies using AEE relative to body weight compared to studies using absolute AEE. This would support the hypothesis that body weight is a relevant factor for AEE prediction, either by including it as a prediction factor or by standardizing AEE on body weight.

Other minor limitations may have affected the variance in AEE explained by accelerometry, which could potentially have contributed to greater heterogeneity: in two articles, lacking information about accelerometer type, body position or wear time was substituted based on information from other references that used the same accelerometer device [90, 193]; in three studies, time periods of DLW measurement and accelerometry recording did not overlap completely [186, 191, 194]. Overall, the pooling of heterogeneous studies into groups may have attenuated between-group differences towards the null.

To improve the prediction of free-living AEE based on accelerometer-derived PA one focus should be on the improved assessment of PA by use of advanced accelerometer technique and data analysis [108], and another focus should be on additional factors beyond PA that may affect AEE. Unfortunately, the findings of this review do not allow evidence-based recommendations on how to improve AEE prediction. Therefore, future studies are needed to examine in detail how AEE can best be predicted based on accelerometry and which factors should be considered.

To sum up, the explained variance of predicted AEE by accelerometer output varied broadly across studies, tended to be higher in studies with smaller sample size, and was significantly improved by including other factors beyond accelerometry independent of the number of additional predictors. To overcome the limitations and improve the prediction of AEE in population-based studies, future studies should focus on improved PA assessment in free-living conditions by continue development in accelerometry methods with focus on comparability and transparency, or find possibilities to combine objective and subjective information on PA, and figure out which additional predictors are the most important for particular populations.

6.2 Development of AEE prediction models based on accelerometry-derived physical activity

This present thesis aimed at developing prediction models for free-living AEE using stepwise selection regression based on most appropriate PA parameters derived from triaxial accelerometry, and additional predictors derived from measurements of anthropometry, body composition, blood pressure or dietary intake, and PA questionnaires (IPAQ, QUAP). Alternative prediction models were provided for different variable settings simulating that only a smaller set of candidate variables is available.

Among the PA parameters derived from 2-week accelerometry in the ActivE study, uniaxial *Axis 1 counts* and triaxial *Vector magnitude (VM) counts* were the most appropriate crude PA parameters by explaining the highest proportion of variance in AEE in univariate models (Axis 1 counts R^2 = 34.0 %, VM counts R^2 = 33.8 %). In previous studies, count-based triaxial accelerometer outputs explained 22.0 – 49.0 % of the variance in AEE [181, 183, 185, 194, 195], and count-based uniaxial accelerometer outputs explained 4.3 – 46.0 % of the variance in AEE [90, 181, 183, 187], which is in line with the results found in this study. Another frequently used uniaxial accelerometer output in previous studies was *steps per day*, that tended to explain a slightly lower variance in AEE at 7.5 – 34.2 % [90, 181, 191], compared to 32.4 % in this study.

In this study, additionally, two sets of accelerometer variables were examined that explained a higher proportion of variance in AEE (set 1: R^2 = 36.1 %; set 2: R^2 = 35.3 %) compared to the best single accelerometer parameter models, and did not cause multicollinearity problems proved by low VIF values (set 1: 1.29 – 1.65; set 2: 1.05 – 1.09). However, the adjusted explained variance was lower compared to the best single accelerometer parameter models (set 1: adjusted R^2 = 31.8 %; set 2: adjusted R^2 = 30.9 %). Further, one single variable that

adequately represents PA should be preferred in order to avoid overfitting and to keep the number of predictors as low as possible due to the limited number of observations in this study [222]. Moreover, in both sets the accelerometer variables were forced to be included together in the prediction models, while the single parameters, *VM counts* and *Axis 1 counts*, were offered for selection and were always selected as the first predictor in all developed AEE prediction models.

Including a second parameter in the model in addition to *VM counts* or *Axis 1 counts*, body composition and anthropometric variables, such as *fat-free mass* (measured by ADP or BIA) or *height*, added the highest proportion of explained variance in AEE (19.2 – 26.7 %) resulting in a range of 53.3 – 60.5 % in total explained variance in these models. The same two-parameter models emerged during the main-selection step when reduced variable settings were examined. These findings are comparable to prediction models of previous studies using a triaxial accelerometer, where *fat-free mass* was selected as second predictor in addition to accelerometer output, and the model explained 53.0 % [185] and 60.0 % [186] of the total variance in AEE. Interestingly, in the present and in previous studies, *fat-free mass* and *height* were never included together in a model [185-190], probably due to the strong relation between these variables (based on their relation to *sex*) that would have induced multicollinearity problems. Furthermore, both predictors are physiologically plausible: *fat-free mass* refers to the skeletal muscle mass and represents the site of energy consumption as a consequence of PA [11, 26, 236]; and similarly, *height* reflects the sex-based differences in *fat-free mass* as well.
In some previous studies *height* was included in combination with *body weight* [188, 190], which comprises *fat mass* and *fat-free mass*. But in this study *weight* was not selected during the statistical-based preselection step of the anthropometry variable group, and was therefore not offered for selection to build the final AEE prediction models.

In this study, having *VM counts* from accelerometry and the full set of (preselected) variables available, the predictors *VM counts*, *fat-free mass by ADP*, *time in moderate PA and walking* (derived from IPAQ) and *carbohydrate intake* were selected using stepwise regression and explained 70.7 % of variance in free-living AEE. An alternative 'full variable set' model revealed the same selected predictors as above plus *time spent sitting* and *time in locomotion* (both derived from QUAP) and explained 75.4 % of variance in AEE. Having *Axis 1 counts* from accelerometry and the full set of (preselected) variables available, the same predictors as above where selected and explained 70.8 % of variance in AEE.

In reduced variable settings (having a smaller number of preselected variables available), *fat-free mass by ADP* was substituted by *fat-free mass by BIA* (if no ADP was available) or *height* (if no measurement of body composition was available), which again emphasizes the relevance of variables of body composition and anthropometry for AEE prediction.
Other selected predictors (*time in moderate PA and walking*, *time spent sitting*, *time in locomotion*, *carbohydrate intake*, *resting heart rate*) contributed a much lower, but usually significant proportion ranging from 2.3 – 9.7 % to explain additional variance in free-living AEE.

In this study, the preselected candidate variable *sex* was not selected as a predictor in any developed model in the considered variable settings during the main-selection step. This could be explained by the strong association of *sex* with *fat-free mass* and also with *height* [238]. Thus, although *sex* is associated with AEE [26], which was also confirmed in the univariate regression and correlation analysis in this study, this association might have been already reflected in a large proportion by including *fat-free mass* or *height* in the prediction models. In comparable studies using stepwise selection regression, *sex* was not selected when *height* or *fat-free mass* was included in the model [185, 186]. Including *sex* as second parameter in addition to *VM counts* or *Axis 1 counts* (two-parameter models), *sex* added a significant proportion of explained variance in AEE (14.7 % / 15.4 %) resulting in a total explained variance of 48.5 % and 49.4 %, respectively. This suggests that *sex* would be a plausible predictor for AEE, if no information about body composition or anthropometry is available. However, in this study, such a scenario of variable setting was not considered for the main selection step, because at least *height* was assumed to be always available, since it is a standard parameter in epidemiological studies and easy to collect via measurement or self-report.

Similarly, *maximum handgrip strength* was not selected as a predictor in any developed model in the considered variable settings during the main-selection step in this study. *Handgrip strength* is an indicator for muscle strength as one component of physical fitness [11]. It is predominantly determined by *sex* due to greater muscle mass and consequently greater *fat-free mass* in men compared to women [239, 240], which was also observed in this study. Thus, although *maximum handgrip strength* was associated with AEE in the univariate analysis that was probably driven by *sex* (because the association disappeared when adjusted for *sex*), again, this association might have been already reflected in a large proportion by including *fat-free mass* or *height* in the prediction models. Unfortunately, no comparisons with previous studies are possible, since this parameter has not yet been taken into account for AEE prediction. Nevertheless, including *maximum handgrip strength* as second parameter in

addition to *VM counts* or *Axis 1 counts* (two-parameter models), it added a significant proportion to explain variance in AEE (15.2 % / 15.0 %) resulting in a total explained variance of 48.9 % and 49.0 %, respectively. This suggests that also *maximum handgrip strength* would be a plausible predictor for AEE, if no information about body composition, anthropometry or sex is available. As mentioned above, such a scenario of reduced variable setting was not examined in this study.

Resting heart rate was selected in very few prediction models and always as last predictor, although this parameter was available in every examined variable setting during the main-selection step. Further, the contribution to improve explained variance in AEE was quite small (2.5 – 4.8 %). Included as second parameter in addition to *VM counts* or *Axis 1 counts* (two-parameter models), *resting heart rate* added a small and marginally significant proportion to explain variance in AEE (6.6 % / 5.5 %). This suggests that the relevance of *resting heart rate* in AEE prediction might be questionable. Nevertheless, it is an easy-to-measure parameter and might indicate overall fitness levels, with people at high fitness levels showing lower values [241], which was demonstrated in this study by an inverse association between *resting heart rate* and AEE. Unfortunately, no comparisons with previous studies are possible, since this parameter has not yet been taken into account for AEE prediction.

In addition to objective PA assessment using accelerometry, self-reported information about PA was obtained from questionnaires and considered in the analysis in this study. The variable *time in moderate PA and walking* (derived from IPAQ) was always selected as predictor during the main-selection step, if information from IPAQ was available in the variable setting, and contributed moderately to improve explained variance in AEE (4.7 – 9.7 %). The variable *time in locomotion* (derived from QUAP) was often selected in VM counts models, but less frequently in Axis 1 counts models, if information from QUAP was available in the variable setting. However, the contribution to improve explained variance in AEE was small (2.4 – 4.4 %). Included as second parameter in addition to *VM counts* or *Axis 1 counts* (two-parameter models), both *time in moderate PA and walking* and *time in locomotion* did not add any significant proportion to explain variance in AEE (0.7-3.1 %).

In terms of content, nevertheless, the selection of both predictors seems plausible, since they may include information about activities that were not adequately captured by the accelerometer, such as cycling, or moderate static exercises (e.g. gymnastics, yoga), household or water activities, or walking with light weights [15], which is relevant for AEE prediction. This suggests that additional information about PA from questionnaires could be useful to improve

the prediction of AEE, although the effort to obtain the information has to be considered, as well as general limitations of questionnaires, such as recall bias, social desirability bias, or information bias due to misinterpretation of questions, which could lead to over- or underestimation of duration and intensity of PA resulting in inaccurate and unreliable quantitative information [18, 41, 102, 103].

The variable *time spent sitting* (derived from QUAP) was often selected as predictor, if information from QUAP was available in the variable setting, but contributed only a small amount to explain variance in AEE (2.3 – 3.7 %). Included as second parameter in addition to *VM counts* or *Axis 1 counts* (two-parameter models), *time spent sitting* added a small proportion to explain variance in AEE (7.7 % / 7.3 %). The invers association of *time spent sitting* with AEE seems plausible, as in sitting positions people tend to be inactive without substantial energy expenditure, and as more time is spent in sedentary behavior during the day, less time can be used for PA behavior. The results suggest that *time spent sitting* might be useful to improve the prediction of AEE; however, the contribution to improve AEE prediction and the effort to obtain this information were unbalanced in this study. Unfortunately, no comparisons with previous studies are possible, since PA parameters derived from questionnaires in addition to accelerometry have not yet been taken into account for AEE prediction.

Derived from a dietary record, the variable *energy intake* was not selected as a predictor in any developed model in the considered variable settings during the main-selection step. Included as second parameter in addition to *VM counts* or *Axis 1 counts* (two-parameter models), *energy intake* added a moderate proportion to explain variance in AEE (10.0 % / 12.4 %).
The association between *energy intake* and AEE was probably determined by *sex* as substitute for *fat-free mass*, because *energy intake* was associated with *sex* ($r_{Pearson}$= -0.435, p=0.002), and other sex-determined parameters, such as *height*, *fat-free mass*, or *maximum handgrip strength*, but the association disappeared or attenuated in sex-adjusted correlation analysis. Furthermore, under conditions of stable body weight and valid reporting of diet, *energy intake* can be used to estimate total energy expenditure [38, 242], which incorporates AEE as a component, and is itself determined by sex [74], due to the sex-dependent relation of resting energy expenditure based on *fat-free mass*. This suggests that the association between *energy intake* and AEE might have been reflected by including *fat-free mass* or *height* in the prediction models.

On the other hand, *carbohydrate intake* was frequently selected as a predictor during the main-selection step, if nutritional information was available in the variable setting; however, the contribution to improve explained variance in AEE was rather small (2.7 – 4.7 %). Included as second parameter in addition to *VM counts* or *Axis 1 counts* (two-parameter models), *carbohydrate intake*, similarly, added a moderate proportion to explain variance in AEE (8.8 % / 11.1 %).

Although *carbohydrate intake* accounted for the main proportion of daily energy intake in this study (45.3 %), the *absolute* carbohydrate intake was not associated with *sex*. Considered in terms of content, it could be speculated that *carbohydrate intake* might include additional information on PA-related attributes in this study, such that people with certain activity-related attributes differ in their dietary behavior. This would suggest that *carbohydrate intake* might be useful to improve the prediction of AEE assuming a valid reporting of diet; however, the contribution to improve AEE prediction and the effort to obtain this information were unbalanced in this study. Additionally, nutritional information is prone to underreporting, which was also observed in this study indicated by a reduced ratio of energy intake to total energy expenditure (median of ratio = 0.76) [242]. Therefore, results on nutritional aspects should be interpreted cautiously.

The main strength of this study was the large number of potential candidate variables used to develop AEE prediction models; unfortunately, for many of the selected variables no previous comparative studies were available. Further, the grouping of (candidate) variables concerning examination module or context allowed for developing several AEE prediction models for different variable settings. This enables to choose an appropriate model based on the availability of predictor variables that could differ due to missing values or not implemented measurements in the study protocol. For example, in the German National Cohort study, data on 7-day-accelerometry, *fat-free mass* measured by BIA method, anthropometry, and PA information from IPAQ were collected by default from a large population-based sample [177]. Some participants additionally have information on PA derived from QUAP, or nutritional information from food-frequency-questionnaire [177]. Thus, AEE prediction models developed in this study could be applied to this sample to obtain estimates of AEE that can be further used to investigate associations with biomarker concentrations or chronic disease risks.

Another important strength of this study is the 24-hour assessment of free-living PA for 13 days using accelerometry providing a reliable estimate of habitual PA in adults [243]. Both the measurement of PA by accelerometry and the measurement of total energy expenditure by

doubly-labeled water (DLW) method were performed simultaneously, so that recorded PA, theoretically, should be reflected in the derived AEE. Non-wear times of accelerometer during waking hours amounted to about 15 minutes per day (median) according to wearing diary (IQR: 0 – 25 minutes per day), which is very low and therefore not to be expected to influence the accelerometer-derived PA outcome significantly.

Further, the ActivE study population covered a large range of age (20 – 69 years) and BMI (18.6 – 36.1 kg/m²) for both sexes, which creates more heterogeneity and variability in the data to promote generalizability of study findings, although it was a convenience sample. The analytic sample size was adequate (n=49) and comparable to previous studies of similar study design (using DLW) and aim [185, 191, 195], but results on predictor selection might be limited due to high number of candidate variables (m=76). To overcome this limitation, first, a multi-step selection approach was carried out to develop AEE prediction models using a conceptual-based preselection for accelerometry variables, and stepwise selection regression for the remaining variables. Second, rigorous p-value limits ($p<0.05$) were chosen for the partial F-statistic for including and retaining variables during the stepwise selection regression, in order to restrict the number of selected variables, so that primarily variables with potentially stronger effects were selected, and thus also to prevent overfitting [222]. Third, to investigate the stability of the developed AEE prediction models, the main-selection step was repeated using alternative variable selection techniques, such as forward selection, backward elimination, LASSO selection, and bootstrap sampling; and developed AEE prediction models were recalculated after excluding influential observations from the analytic sample.

The sensitivity analyses revealed that the AEE prediction models developed by stepwise selection seem basically robust, since the same predictors were selected using forward selection or backward elimination except for minor differences. In bootstrap samples, stepwise selection revealed that accelerometer-derived variables (*VM counts* or *Axis 1 counts*), body composition or anthropometry variables (*fat-free mass* from ADP/BIA or *height*), and in part the questionnaire-derived PA variable *time in moderate PA and walking* were the most important predictors for AEE [227]. LASSO selection revealed a selection of more predictors compared to stepwise selection, which might cause problems of overfitting and multicollinearity [222], and also suggests that the stepwise regression approach provided reliable results in this study, despite of common limitations of this variable selection technique such as biased small p-values [221, 244]. An external validation would be required to finally evaluate the reliability of the developed prediction models.

The main limitation of this study was the use of the proprietary accelerometer outputs 'activity counts' provided from the software, which is an abstract measure that varies between different monitors from different manufacturers, and is therefore not comparable between different devices [18, 98, 107]. Thus, the developed prediction models are basically limited for the use of ActiGraph's® GT3X+ derived counts; measurements from other devices would initially have to be validated for this device before the prediction models can be used. Ideally, a comparable measure, such as raw acceleration data, should be used for analysis or model development, whereby all filter and processing steps of the acceleration signals should be considered in a transparent and comprehensible way; however, this will increase the complexity of the analysis [245].

Another limitation is that wearing one accelerometer placed at the hip cannot capture all human activities properly, such as cycling, carrying heavy loads or lifting weight, incline walking, or upper body movements, which is a general limitation of accelerometers [18, 40, 41, 102]. Consequently, an inaccurate assessment of some activities could lead to underestimation of PA and might have influenced the association to energy expenditure [18, 40, 42].

Further, deviations from study protocol could have resulted in measurement errors for the variables considered, which might have influenced the association between variables and AEE, and thus the probability of variable selection for AEE prediction models. Assuming non-differential errors that do not depend on values of other variables, this would attenuate effect estimates toward the null [246].

To sum up, accelerometer-derived PA parameters (*VM counts, Axis 1 counts*) and *fat-free mass* explained most of the variance in AEE. Alternatively, *height* from anthropometry is an adequate substitute for *fat-free mass*. The explained variance in AEE can be further improved by questionnaire-based information about PA, carbohydrate intake, and resting heart rate; however, the effort to obtain the information has to be considered in view of the limited amount of improvement.

To improve the prediction of AEE based on accelerometry-derived PA, future studies should focus on improving habitual PA assessment via accelerometry by continuing to develop technology (e.g. use of multi-sensor devices without affecting daily life and wearing comfort), integrating complex raw acceleration signals to provide comparable and device-independent data, ideally combined in one output measure, improving the detection of specific activity

types or PA patterns, or combining different objective and subjective PA measurement methods.

6.3 Association of activity parameters with cardiometabolic factors

This part of the present thesis discusses the findings on the association of physical activity (PA) of low, moderate and vigorous intensity, of overall PA and activity-related energy expenditure (AEE) with inflammatory and metabolic markers of cardiovascular diseases. These associations were examined in a secondary analysis based on data of the ActivE study. In this context, questions should be answered as to whether the intensity of PA plays a role in achieving beneficial health outcomes, and whether different intensities of PA have different effects on health outcomes.

In this study, *time in total activity* (independent of intensity) was associated with lower glucose levels; and independent of PA in complement intensity categories, *time in vigorous PA* was associated with lower (log)-CRP levels, and also *proportion of vigorous PA* was associated with lower (log)-CRP levels. Additionally, in separate PA parameter models without mutual adjustment for complement PA intensity categories, *time in moderate PA* was associated with lower glucose levels. These data suggest that for achieving favorable effects in cardiometabolic factors related to glucose homeostasis the overall activity independent of PA intensity might be relevant, with promising contribution of moderate intensity PA; whereas for parameters related to inflammatory responses the intensity of PA might play a determining role, with significant contribution of vigorous intensity PA.

Many previous cross-sectional studies investigated accelerometry-derived PA intensity categories in relation with various cardiometabolic factors, but most of them did not differentiate between PA of vigorous and moderate intensity, but used the combined category moderate-to-vigorous PA (MVPA). This also reflects the openly formulated PA guidelines given by WHO that recommend to spend 150 minutes per week in moderate intensity PA, or 75 minutes in vigorous PA or an equivalent combination regarding intensity and duration of PA [130]. Thus, this study cannot exactly be compared to other studies because of different consideration of PA intensity categories. In addition, this study is the one first that has investigated time spent in total activity regardless of intensity category.

One study in U.S. adults (NHANES 2003-2006) that used distinct intensity categories for moderate and vigorous PA, found an inverse association between moderate PA and CRP levels,

but not with vigorous PA [152]. However, using the combined category MVPA, many studies conducted in different populations reported that more time in MVPA was associated with lower CRP levels [136, 149, 153, 158, 160, 161, 247, 248], but not all associations were independent of complement intensity categories [161, 248]. Some studies also found an inverse association between low intensity PA and CRP levels [149, 151-153, 248], even independent of complement intensity categories [151, 153]. Other studies that considered complement intensity categories by mutual adjustment or isotemporal substitution [249] found no association between low intensity PA and CRP levels [136, 149, 247], which was consistent with results presented in this thesis.

The possible acute and long-term mechanisms by which PA could affect the concentration of circulating CRP and other inflammatory markers have been described in several reviews. These include an elevated release of anti-inflammatory cytokines (e.g. IL-6 from skeletal muscle tissue, IL-10), and a lower production and release of pro-inflammatory cytokines (e.g. TNF-alpha, IL-1beta) from various immune cells and adipose tissue, especially visceral adipose tissue, whose mass can be additionally reduced by a negative energy balance due to PA [162, 250-252].

Regarding (fasting) glucose levels, one study that used distinct intensity categories for moderate and vigorous PA, found an inverse association with moderate PA, but not with vigorous PA [152], which was consistent with the results of separate PA parameter models in this thesis (when complement intensity categories were not considered). In the mutually adjusted models this inverse association was of similar strength, but lost statistical significance.

In previous studies using the combined category MVPA, results were inconsistent; some studies found an inverse association of MVPA with glucose levels [153, 159, 160, 247, 253], some found no association [136, 150, 151, 157, 158, 248], both with and without considering for complement intensity categories. This inconsistency might indicate that a differentiation between moderate and vigorous PA could be important to find out which intensity category creates (greater) beneficial effects on glucose levels, and thus to derive appropriate public health recommendations. On the other hand, if PA intensity would be less important than time in total activity regardless of intensity, associations would have been expected in the combined category MVPA that accounts for a greater proportion of total activity compared to the single categories, or even low intensity PA that accounts for the greatest proportion of daily PA. But no association was found between low intensity PA and glucose level in the present study and in most previous studies [136, 150-153, 247, 248, 253, 254].

However, *time in total activity* was inversely associated with glucose level in this study, which could be due to the fact that the ActivE study participants spent on average more time in moderate PA (98 minutes/day, range 53 – 164 minutes/day) and in vigorous PA (21 minutes/day, range 6 – 51 minutes/day) compared to similar study populations from NHANES (12 – 41 minutes/day in moderate PA, 0.1 – 1.9 minutes/day in vigorous PA [255]; 19 minutes/day in MVPA [256]). However, in NHANES (2003-2006) a uniaxial accelerometer was used and activity counts cut-off values for intensity categories differed slightly compared to this study.

One previous study used total activity counts as measure for total activity, but found no association with glucose level [158]. Compared to this study, the discrepancies in the results might be explained by methodological differences; *Swindell et al*. used a different accelerometer device for only 4 – 7 days and a different PA outcome based on all detected activity counts, and examined a prediabetic study population [158].

Regarding other factors related to glucose homeostasis, this study additionally investigated insulin, HOMA index (measure of insulin resistance [257]), HbA_{1c} and C-peptide (marker for insulin production and release), which were all drawn from fasting blood samples. In this thesis, the results of age- and sex-adjusted spearman rank correlation analysis revealed an inverse association of *time in vigorous PA* with insulin and also with HOMA index, but this could not be revealed in regression analysis for any intensity category.

One previous study using distinct PA intensity categories found an inverse association between moderate PA and insulin, but without considering for complement intensity categories [152]. Further, many previous studies found an inverse association between MVPA and insulin [136, 153, 157-160, 247], as well as HOMA index [136, 153, 157-159, 247]; and also between low intensity PA and insulin [136, 152, 153, 247], as well as HOMA index [136, 152, 153, 247], but not all of them considered for complement intensity categories [136, 152, 159], or when they did the association lost significance [136].

The fact that many studies found an association both with MVPA and low intensity PA, suggests that each intensity might have beneficial effects on insulin and HOMA index (which considers levels of insulin and glucose), and that also total activity, as the sum of these categories, should have beneficial effects. In this study, only borderline significant association were found between *time in total activity* and HOMA index in the separate PA parameter models (p=0.063), in the mutually adjusted PA parameter models (p=0.095), and in Spearman rank correlation analysis (p=0.054). One previous study that used total activity counts as measure for total activity found an inverse association with insulin and HOMA index [158].

The factors HbA_{1c} and C-peptide were barely investigated in previous studies. While in the present study no associations were found between PA in any intensity category or overall PA and HbA_{1c} or C-peptide, in previous studies, results on HbA_{1c} and MVPA were inconsistent (one study found an inverse association with MVPA [160], two studies found no association with MVPA [150, 158]); and no association was found with low intensity PA [150]. Regarding C-peptide, one study reported an inverse association with MVPA that was attenuated and lost statistical significance when complement intensity categories were considered [160].
The possible mechanisms by which PA could affect homeostasis of glucose and its related factors have been described in several reviews. These include an improved insulin sensitivity as a result of an increased glucose uptake in the skeletal muscle by PA-stimulated translocation of GLUT4 transporters, an increased concentration of GLUT4 transporter in the muscle, an increased capillarization and thereby increasing metabolic efficiency of the skeletal muscle, and a reduction of visceral body fat [155, 250, 258].

Regarding factors related to lipid metabolism, this study investigated total cholesterol, HDL cholesterol, LDL cholesterol, HDL/cholesterol ratio, and triglycerides, which were all drawn from fasting blood samples. Many previous studies on HDL cholesterol found a positive association with MVPA [136, 151, 159, 160, 247, 248, 253], in part with considering complement intensity categories [136, 160, 247, 253]; whereas some studies found no association [150, 158, 161]. In one previous study using distinct intensity categories, both moderate and vigorous PA were positively associated with HDL cholesterol [152]. Inconsistent results were found on the association of low intensity PA and HDL cholesterol, some studies found a positive association [248, 254], but only in separate PA parameter models [247], or only for the higher range of low intensity PA [152]; and other studies found no association [136, 150-152, 247, 253].
In this thesis, the results of the age- and sex-adjusted spearman rank correlation analysis revealed a positive association of absolute *time in vigorous PA* and of *proportion in vigorous PA* with HDL cholesterol, but this could not be revealed in regression analysis for PA in any intensity category or overall PA.

Regarding total cholesterol and LDL cholesterol, most of the studies found no association both with MVPA [136, 151, 152, 158, 160, 161, 247, 248], and with low intensity PA [136, 151, 152, 247, 248]. One study with adults of a large age range found an inverse association of MVPA with both total cholesterol and LDL cholesterol, but without adjustment for complement intensity categories [159].

Regarding triglycerides, inconsistent results were found in previous studies using the combined category MVPA; some studies found an inverse association with triglycerides [158, 159, 161, 247, 253], of which two findings were only in the separate PA parameter models [136, 160]; and some studies found no association [136, 150, 151, 160, 248]. One previous study using distinct intensity categories, found an inverse association with moderate PA, but not with vigorous PA [152]. Further, many studies found an inverse association with low intensity PA [136, 152, 247, 248, 253, 254], which could not be confirmed in this study, as well as in other previous studies [150, 151].

The possible mechanisms by which PA could affect the regulation of blood lipids have been described in several reviews. These include a general improvement of body composition, in particular a reduction of visceral fat mass, as well as an increased capacity of fatty acid metabolization due to adaptations in skeletal muscle, and reduction of apolipoprotein-B levels [250, 259, 260].

The effect of different PA intensity levels on favorable health outcomes has also been investigated in intervention studies under controlled conditions implementing specific activities, such as (treadmill) walking, exercising (on ergometer), or interrupting and exchanging sedentary behavior with standing or walking. Favorable effects have been confirmed on HDL cholesterol by more time in MVPA [261-264], on total cholesterol by more time in vigorous PA [264] and low intensity PA [265], on triglycerides by more time in MVPA [263] and low intensity PA [265], on glucose by more time in MVPA [266], moderate PA [267], and low intensity PA [266-270], and on insulin by more time in MVPA [266], moderate PA [267], and low intensity PA [265-267, 269-271]. Beneficial effects on glucose and insulin levels were quite consistent among the considered studies, whereas effects on factors of the lipid profile were more inconsistent, with some studies found no effects on HDL by more time in MVPA [272] or low intensity PA [265], on total cholesterol by more time in MVPA [262, 263, 272] or moderate PA [264], on triglycerides by more time in MVPA [262, 272] or low intensity PA [269], or on LDL cholesterol by more time in MVPA [262, 263, 272] or low intensity PA [265].

Similar to total activity counts [158] and *time in total activity* (this study), also AEE can be used as an overall measure for total PA regardless of intensity. In this study, AEE—both measured by DLW and predicted from developed prediction models—was inversely associated with glucose level, and with HOMA index (only predicted AEE), which would confirm the above

mentioned suggestion that for factors related to glucose homeostasis overall PA might be more relevant than specific PA intensity categories.

Previous studies using AEE as overall PA measure found an inverse association with CRP [149], but no association between AEE and insulin, as well as HOMA index [92]. But when evaluated prospectively, (baseline) AEE was associated with insulin levels at follow-up [91], and the change in AEE was inversely associated with insulin and triglycerides [273] regardless of fitness level and obesity or body fat, respectively. The discrepancies in the results might be explained by methodological differences between the studies (cross-sectional vs. prospective design with 5 years of follow-up, AEE derived from 14 days DLW measurement vs. AEE derived from 4 days' heart-rate monitoring using flex-point approach, sample size).

An important strength of this study is the 24-hour assessment of PA using accelerometry recording 13 days of free-living activities, which covers the maximum waking time, and provides a reliable estimation of habitual PA in adults [243]. In this study population accelerometer non-wear times during waking hours amounted to about 15 minutes per day (median) according to wearing diary (IQR = 0 – 25 minutes per day), which is very low and therefore not to be expected to influence the accelerometer-derived PA outcome significantly.

Another strength of this study is the adjustment for complement intensity categories in the multiple PA parameter models, that would show the effect of change in one PA category when the other categories remain unchanged. But because one day consists of a finite amount of time, each shift in one category would automatically lead to a shift in another category. According to the isotemporal substitution model approach, the results in this study reflect the effect exchanging inactivity in favor of low, moderate or vigorous PA, respectively [249]. While in this study inactivity refers to periods of 0 – 78 cpm activity level and includes sleeping and sedentary behavior, other studies additionally differentiate between time in sleeping and sedentary behavior and investigated the effects of exchanging sitting or sleeping in favor of PA, respectively [150, 247].

Further, this is one of few existing studies that investigated the time spent in total activity regardless of intensity, and that examined the distinct categories of moderate and vigorous PA rather than the commonly used combined category MVPA.

Although the analytic sample size was low (n=50), the main findings associating *time of vigorous PA* with lower CRP levels, and *time in total activity* with lower glucose levels, seem robust as they remained significant in the context of sensitivity analyses when subjects were excluded due to interfering medications, outlier values, or detection as influential observations. Further, the ActivE study participants covered a large range of age (20 – 69

years) and BMI (18.6 – 36.1 kg/m²) for both sexes, which creates more heterogeneity and variability in the data to promote generalizability of study findings, although it was a convenience sample.

On the other hand, there are limitations that should be taken into account when interpreting the results. First, the cross-sectional study design does not allow any conclusions on causality between PA intensity levels and cardiometabolic factors. Further, this study is a secondary analysis; therefore, the sample size might not be adequate to reveal enough statistical power for more precise and significant associations.

Regarding PA assessment, one accelerometer placed at the hip is not able to capture all human activities properly, such as cycling, carrying heavy loads, incline walking, or upper body movements, which is a general limitation of (hip-worn) accelerometers [18, 40-42, 102]. Consequently, an inaccurate assessment of some activities could lead to an underestimation of time in PA in total or in specific intensity categories. Further, participants were asked to remove the accelerometer for water activities and activities with high body contact, which would also lead to an underestimation of time in PA. Although no relevant non-wear-time was detected (except for one participant with one excluded day), potentially, each non-wear-time is included in the PA data, and would always be counted as inactivity (0 – 78 cpm), instead of contributing to low, moderate, or vigorous PA depending on the actual performed activity. This potential underestimation of time in PA in total or in the specific intensity categories might have affected the corresponding association to cardiometabolic factors.

Although potential confounders (such as sex, age, BMI, smoking status and alcohol consumption) were considered in the analysis, residual confounding due to unmeasured factors might still have influenced the results. Further, multiple statistical tests were performed that increased the cumulative chance of false-positive results.

To sum up, the findings of this secondary analysis suggest that for achieving favorable effects in cardiometabolic factors related to inflammatory responses the intensity of PA might play a determining role, especially high intensity PA for CRP levels; whereas for parameters related to glucose homeostasis overall PA regardless of intensity levels is relevant, but with promising contribution of moderate intensity PA. To evaluate and confirm these findings, future studies should not only focus on the distinct PA intensity categories of the whole spectrum, but also on measures of overall PA, such as total activity counts, accumulated time in the different PA intensity categories or AEE.

Despite the complex and challenging measurement of PA and the lack of a feasible gold standard method, measurement errors in PA assessment could be reduced by repeated measurements with prospective approaches, or combining different objective and subjective methods.

6.4 Conclusion and Outlook

This thesis represents the first comprehensive investigation of 76 potential predictors for modeling free-living activity-related energy expenditure (AEE) in adults based on 2-weeks assessment of physical activity by accelerometry. To develop AEE prediction models for free-living conditions the ActivE-study was designed, deriving AEE from the assessment of total energy expenditure (TEE) via doubly-labeled water method, resting energy expenditure via indirect calorimetry and diet-induced thermogenesis globally estimated as 10 % of TEE.

The crude count-based accelerometer outputs, *Vector magnitude counts (per minute)* and *Axis 1 counts (per minute)*, provided robust estimates of physical activity for AEE prediction by explaining the highest proportion of the variance in AEE. In addition, information of body composition or anthropometry provides essential improvement of AEE prediction, with fat-free mass accounting for the greatest contribution, and height being an appropriate substitute. These two groups of variables seem most relevant for predicting AEE as demonstrated by the consistent findings of this and previous studies, but other predictors could further contribute to improve the prediction of AEE. This study revealed that additional information of physical activity derived from questionnaires and information about carbohydrate intake contributed a small but significant proportion to explain additional variance in AEE. However, the effort in obtaining these variables and the benefit in AEE estimation have to be considered for these groups of variables. For practice, if these variables are readily available, they may provide a good option for AEE prediction to be considered, but it might be disproportionate to collect this extra information just aiming at improving the prediction of AEE in a study population.

Based on the developed prediction models in this study, the association of AEE with cardiometabolic factors as indicators for chronic disease risk was investigated. The observed inverse association of AEE with glucose levels and with HOMA index suggests that an increase of total physical activity regardless of intensity levels might have beneficial effects on glucose homeostasis. This finding agreed with the observed inverse association of time spent in total activity (accumulating time spent in activity of low, moderate and vigorous intensity levels) with glucose levels. On the other hand, the observed inverse association between time in

vigorous physical activity and CRP levels suggests that for cardiometabolic factors or disease outcomes related to inflammatory responses the intensity of physical activity might play a significant role having greater beneficial effects with increasing intensity level.

All investigations of the present thesis were centered on the measurement of physical activity by means of accelerometry, a recently introduced objective method for the assessment physical activity. To improve the prediction of AEE, as well as the investigation of association between physical activity related behavior and disease outcomes, an accurate determination and description of habitual physical activity in all its dimensions and aspects is necessary. The ongoing development of activity recording monitors regarding technology, data processing, or implementation of algorithms to analyze complex data seems promising. Advanced modeling methods in the field of machine learning techniques, such as artificial neural network, hidden Markov modeling or decision trees, could promote and improve the classification of types of physical activity, and the identification of activity patterns, which could improve the prediction of related energy expenditure [98, 119, 123, 274]. In this regard, switching from count-based approaches to raw acceleration data-based analysis might be useful for this application [245].
On the other hand, general agreements on the processing steps of recorded acceleration signals (e.g. filtering, amplifying, and integration of signals) and the reporting of accelerometer outputs would be preferable to allow for comparisons between different monitors or studies [98]. Due to the large heterogeneity the comparability between accelerometry-based studies and the validity of pooled analyses is often limited, which was observed in the systematic review presented in this thesis.

From the public health perspective, to establish sufficient recommendations an accurate assessment of physical activity is essential to detect differences and changes of PA over time within and between populations, to quantify dose-response relationships and investigate (causal) associations between physical activity characteristics (including derived measures like predicted AEE) and health outcomes, or to evaluate intervention programs [41, 103].
This also includes investigations into high-risk sedentary behavior or inactivity, and how and to what extent sedentary behavior can be reduced by replacing inactive time with (primarily low intensity) physical activity [138, 275, 276].

7 Summary

Assessment of physical activity (PA) is a great concern in epidemiological and public health research, since the extent of PA plays an important role in the etiology of numerous chronic diseases and all-cause-mortality, and as modifiable lifestyle factor PA is a favored target for disease prevention and health promotion. However, less is known about the relation of activity-related energy expenditure (AEE) and chronic disease risk. AEE is defined as energy expenditure increase due to PA, which is the bodily movement involving skeletal muscle contraction. Since AEE assessment under free-living condition is challenging, traditionally, AEE was derived from questionnaire-based PA information linked to energy equivalents. Advancements in the field of PA assessment allow to capture acceleration signals due to body movement revealing objective and more accurate quantitative information about intensity, frequency and duration of PA. Similarly, accelerometry-based PA information can be converted to AEE using device-specific algorithms, considering additional individual factors such as sex, age, height, or weight. However, it is unclear to what extent accelerometry-derived PA can explain the variance in AEE under free-living conditions, and to what extent additional individual characteristics could improve the estimation of energy expenditure.

This thesis aimed to develop prediction models to estimate free-living AEE based on accelerometry-derived PA parameters. Therefore, first, previous studies on AEE prediction were systematically reviewed investigating to what extent accelerometer-derived PA outputs and additional parameters explain and improve the variance in free-living AEE, respectively; second, prediction models estimating free-living AEE were developed based on accelerometry-derived PA parameters and additional parameters; and third, the association of (predicted) AEE and accelerometry-derived PA parameters with cardiometabolic factors as indicators for chronic diseases was examined.

For the systematic review, MEDLINE database was searched for studies that estimated AEE based on accelerometry-derived PA in adults under free-living conditions (using doubly-labeled water method), resulting in 28 eligible studies. The variance of AEE explained by accelerometer-derived PA output ranged from 4 – 80 % (median crude R^2 = 26.0 %). Across studies, sample size ranged from 10 to 149, and was inversely related to the explained variance. Inclusion of 1 to 3 other predictors in addition to accelerometer output significantly increased the explained variance to a range of 12.5 – 86.0 % (median total R^2 = 41.0 %). These findings suggest that accelerometry-based AEE prediction should be interpreted with caution due to heterogeneity across studies. Including additional predictors beyond accelerometry can

improve the explained variance in AEE, where the type seems more relevant than the number of added predictors.

To develop AEE prediction models based on accelerometry-assessed PA data under free-living conditions, the cross-sectional ActivE study assessed PA over 14 days using the hip-worn triaxial accelerometer Actigraph GT3X+, and simultaneously total energy expenditure (TEE) using the doubly labeled water method in 50 volunteers. Further, resting energy expenditure (REE, by indirect calorimetry), anthropometry, body composition (by BIA and ADP), blood pressure, handgrip strength were measured; sociodemographic and lifestyle factors, PA of previous 7 days (IPAQ) and previous 12 months (QUAP), and 7-day dietary records were assessed; and a blood draw was analyzed for cardiometabolic factors. AEE was calculated as TEE – REE – diet-induced thermogenesis (estimated as 10 % of TEE). Accelerometer output was converted to counts per minute of the single vertical axis (Axis 1 counts) and the combined vector sum of all three axes (vector magnitude (VM) counts) using ActiLife software. Based on VM counts, time spent in PA of low, moderate and vigorous intensity was calculated using an adapted version of the 'Freedson Adult VM3 (2011)' algorithm, and subsequently deriving accumulated time in total activity, and relative proportion of each intensity category.

In a multistep selection approach candidate variables were grouped with regard to context, and each group was regressed on AEE (conceptual-based preselection for the group of accelerometer-derived variables, statistical-based preselection (stepwise regression with $p<0.05$) for the other variable groups). Prediction models of AEE were developed based on all preselected variables (m=11) offered for a second stepwise selection. Alternative models were developed simulating that only a reduced set of predictive variables is available. Sensitivity analyses using different variable selection techniques (forward selection, backward elimination, LASSO selection) and bootstrap sampling were run. To investigate the association of AEE and PA duration and intensity with cardiometabolic factors of inflammation, glucose and lipid metabolism, linear regression analysis was performed, fitting blood levels of total cholesterol, HDL-cholesterol, LDL-cholesterol, (log-)triglycerides, cholesterol-HDL-ratio, glucose, (log-)insulin, HbA_{1c}, C-peptide, (log-)HOMA index and (log-)CRP as outcome variables, with accelerometer-derived PA parameters (time in low intensity PA, time in moderate PA, time in vigorous PA, and time in total activity) as independent variables adjusted for sex, age, BMI, smoking status and alcohol consumption.

Axis 1 counts and *VM counts* explained 34.0 % and 33.8 % of the variance in AEE, respectively. Stepwise selection revealed that 70.7 % of variance in AEE was explained by *VM counts*

(33.8 %), fat-free mass by ADP (26.7 %), *time in moderate PA and walking* (IPAQ, 6.4 %) and carbohydrate intake (3.9 %); and in an alternative model, 75.4 % of variance in AEE was explained by the same predictors plus *time spent sitting* (QUAP, 2.3 %) and *time in locomotion* (QUAP, 2.4 %). Results were similar for Axis 1 counts models. In reduced variable settings (having a smaller number of preselected variables available), *fat-free mass by ADP* was substituted by *fat-free mass by BIA* (if no ADP was available) or *height* (if no measurement of body composition was available), explaining 24.7 % or 20.0 % of additional variance in VM counts models. These findings suggest that accelerometry can provide appropriate PA parameters (*VM counts, Axis 1 counts*) for AEE prediction that can be essentially improved by information of body composition (*fat-free mass*) or anthropometry (*height*). Additional questionnaire-based information about PA, carbohydrate intake, and resting heart rate can further improve the explained variance in AEE; however, the effort to obtain the information has to be considered in view of the limited amount of improvement of explained variance.

Further, ActivE study participants spent 130 minutes per day in low intensity PA, 98 minutes in moderate intensity PA, and 21 minutes in vigorous intensity PA, resulting in 250 minutes of total activity. There was an inverse association of AEE, *time in total activity* (independent of intensity), and *time in moderate PA* (regardless of mutual adjustment for complement PA intensity categories) with glucose levels, an inverse association of *time in vigorous PA* and *proportion of vigorous PA* with (log-)CRP levels, and an inverse association of (predicted) AEE with (log-)HOMA index. These findings suggest that for achieving favorable effects in cardiometabolic factors related to glucose homeostasis the overall activity independent of intensity levels might be relevant, with promising contribution of moderate intensity PA; whereas for parameters related to inflammatory responses the intensity of PA might play a determining role, with significant contribution of vigorous intensity PA.

The improvement of PA assessment in free-living conditions using accelerometry seems promising with the ongoing development of technology, data processing, advanced modeling methods and algorithms to process and analyze more complex ‘raw’ acceleration data. General agreements on accelerometer signal processing and data reporting would increase comparability between studies and validity of pooled analyses. Finally, an accurate quantitative assessment of PA allows for an improved quantification, characterization and prediction of AEE, an improved quantification of dose-response relationships and (causal) associations between PA characteristics (including AEE) and health outcomes, which is essential to establish sufficient public health recommendations.

8 Zusammenfassung

Körperliche Aktivität (KA) ist in der epidemiologischen und gesundheitspolitischen Forschung von großer Bedeutung. Das Ausmaß der KA spielt eine wichtige Rolle bei der Entstehung zahlreicher chronischer Erkrankungen sowie für die Gesamtmortalität, und als modifizierbarer Lebensstilfaktor stellt KA einen bevorzugten Ansatzpunkt zur Krankheitsprävention und Gesundheitsförderung dar. Über die Rolle des aktivitätsabhängigen Energieumsatzes (AEE) und seine Beziehung zu chronischen Erkrankungen ist jedoch wenig bekannt. AEE wird definiert als die Erhöhung des Energieumsatzes aufgrund von KA, das heißt von Körperbewegung, die auf einer Kontraktion der Skelettmuskulatur beruhen. Da die Messung des AEE unter Alltagsbedingungen methodisch sehr aufwendig ist, wurde AEE traditionell aus fragebogenbasierten Erhebungen von KA und deren Zuordnung zu Energieäquivalenten abgeleitet. Neueste Weiterentwicklungen auf dem Gebiet der Erfassung von KA ermöglichen es, Körperbewegungen anhand von Beschleunigungssignalen mittels sogenannter Akzelerometer zu detektieren, und dadurch KA objektiv und mit genaueren quantitativen Informationen zur Intensität, Häufigkeit und Dauer zu erfassen. Aus diesen Akzelerometer-basierten Aktivitätsinformationen können gleichermaßen durch (gerätespezifische) Algorithmen und unter Berücksichtigung von zusätzlichen individuellen Faktoren wie z.B. Geschlecht, Alter, Größe oder Gewicht, Informationen zum AEE abgeleitet werden. Es ist jedoch unklar, inwieweit die Varianz des AEE unter Alltagsbedingungen durch akzelerometrisch erfasste KA erklärt werden kann, und inwieweit zusätzliche Faktoren die Prädiktion des AEE verbessern können.

Das Ziel dieser Arbeit war es Prädiktionsmodelle zur Schätzung des AEE zu entwickeln basierend auf akzelerometrisch erfasster KA. Dazu wurde, erstens, in einer systematischen Literaturübersicht von AEE-Prädiktionsstudien untersucht, inwieweit akzelerometrisch erfasste KA und zusätzliche Faktoren die Varianz des AEE (unter Alltagsbedingungen) erklären und verbessern können; zweitens, Prädiktionsmodelle zur Schätzung AEE entwickelt basierend auf akzelerometrisch erfasster KA und zusätzlichen Parametern; und drittens, der Zusammenhang zwischen (vorhergesagtem) AEE sowie akzelerometrisch erfassten Aktivitätsparametern und kardiometabolischen Faktoren als Indikatoren für chronische Erkrankungen untersucht.

Für die systematische Literaturübersicht wurde die MEDLINE-Datenbank nach Studien durchsucht, die AEE basierend auf akzelerometrisch erfasster KA bei Erwachsenen unter Alltagsbedingungen (d.h. unter Verwendung der doppelt-markierten Wasser-Methode) geschätzt haben. Es wurden 28 geeignete Studien identifiziert. Durch akzelerometrisch erfasste KA wurde 4 – 80 % der AEE-Varianz erklärt (Univariates Modell: Median R^2 = 26,0 %).

Die Teilnehmeranzahl der Studien lag zwischen 10 und 149, und war invers mit der erklärten AEE-Varianz assoziiert. Die Hinzunahme von 1 bis 3 weiteren Prädiktoren zusätzlich zur akzelerometrisch erfassten KA erhöhte die erklärte AEE-Varianz signifikant auf 12,5 – 86,0 % (Gesamtmodell: Median R^2 = 41,0 %). Die Ergebnisse weisen darauf hin, dass die Datenlage zur Prädiktion von AEE unter Alltagsbedingungen basierend auf akzelerometrisch erfasster KA sehr heterogen ist. Die Hinzunahme weiterer Prädiktoren zusätzlich zu KA kann die erklärte Varianz des AEE verbessern, wobei nicht die Anzahl der Prädiktoren, sondern die Art des Prädiktors relevant zu sein scheint.

Für die Entwicklung von AEE-Prädiktionsmodellen basierend auf akzelerometrisch erfasster KA unter Alltagsbedingungen, wurde in der Querschnittsstudie ActivE von 50 Teilnehmern die KA über 14 Tage mittels triaxialem Akzelerometer Actigraph GT3X+, das an der Hüfte getragen wurde, erfasst, und gleichzeitig der Gesamtenergieumsatz (TEE) mit der doppelt-markierten Wasser-Methode gemessen. Außerdem wurden der Ruhe-Nüchtern-Energieumsatz (REE, mittels indirekter Kalorimetrie), Parameter zu Anthropometrie, Körperzusammensetzung (mittels BIA und ADP), Blutdruck, Handgreifstärke, soziodemografische und Lebensstilfaktoren, KA der vergangenen 7 Tage (IPAQ) und der vergangenen 12 Monate (QUAP), Ernährung (mittels 7-Tage Ernährungsprotokoll) erfasst, sowie kardiometabolische Faktoren aus einer Blutprobe bestimmt. AEE wurde berechnet als TEE – REE – Diät-induzierte Thermogenese (geschätzt als 10 % von TEE). Mittels ActiLife Software wurden die Akzelerometersignale in sogenannte Aktivitäts-„Counts“ pro Minute umgewandelt, sowohl für die vertikale Einzelachse, als auch für den Raumvektor (Kombination aller 3 Raumachsen). Basierend auf den Raumvektor-Counts wurde mittels eines adaptierten ‘Freedson Adult VM3 (2011)’ Algorithmus die Zeit in KA mit leichter, moderater und starker Intensität, und daraus die akkumulierte Zeit in Gesamtaktivität sowie die relativen Anteile der jeweiligen Intensitätskategorie berechnet.

In einem mehrstufigen Ansatz zur Variablenselektion wurden die potentiellen Variablen zunächst hinsichtlich Kontext oder Methodik gruppiert und die Variablen jeder Gruppe auf AEE regressiert (konzeptionell basierte Variablenselektion für Gruppe der Akzelerometrie-Variablen, statistisch basierte Variablenselektion (Stepwise Regression mit $p<0,05$) für die anderen Variablengruppen). AEE-Prädiktionsmodelle wurden dann basierend auf den zuvor ausgewählten Variablen (m=11) mittels Stepwise Regression entwickelt. Bei der Entwicklung alternativer Modelle wurde simuliert, dass nur ein reduziertes Variablen-Set zur Verfügung steht. In Sensitivitätsanalysen wurden verschiedene Techniken zur Variablenselektion (Forward Selection, Backward Elimination, LASSO Selection) und das Bootstrap-Sampling angewendet. Um den Zusammenhang zwischen AEE bzw. der Dauer und Intensität von KA mit

kardiometabolischen Faktoren der Entzündung sowie des Glukose- und Lipidstoffwechsels zu untersuchen, wurde eine lineare Regressionsanalyse durchgeführt, in der die Blutkonzentration von Gesamtcholesterin, HDL-Cholesterin, LDL-Cholesterin, (log-) Triglyceriden, Cholesterin-HDL-Verhältnis, Glucose, (log-)Insulin, HbA_{1c}, C-Peptid, (log-)HOMA-Index und (log-)CRP jeweils als abhängige Variable, und die aus dem Akzelerometer abgeleiteten Aktivitätsparameter (*Zeit KA mit geringer Intensität*, *Zeit in KA mit moderater Intensität*, *Zeit in KA mit starker Intensität*, *Zeit in Gesamtaktivität*) als unabhängige Variablen berücksichtigt wurden, jeweils adjustiert für Geschlecht, Alter, BMI, Rauchstatus und Alkoholkonsum.

Die Counts der vertikalen Einzelachse und des Raumvektor erklärten 34,0 % bzw. 33,8 % der AEE-Varianz. Die schrittweise Variablenselektion ergab, dass 70,7 % der AEE-Varianz durch die *Counts des Raumvektors* (33,8 %), *fettfreie Masse* (gemessen durch ADP; 26,7 %), *Zeit in moderater KA und Gehen* (IPAQ; 6,4 %) und *Kohlenhydrataufnahme* (3,9 %) erklärt werden konnte; und in einem alternativen Modell 75,4 % der AEE-Varianz durch die zuvor genannten Prädiktoren plus *Zeit im Sitzen* (QUAP; 2,3 %) und *Zeit in Aktivität zur Fortbewegung* (QUAP; 2,4 %). Ähnliche Ergebnisse zeigten sich für die Modelle mit Einzelachsen-Counts. Wenn eine reduzierte Auswahl an Variablen zur Verfügung stand, wurde *fettfreie Masse aus ADP-Messung* ersetzt durch fe*ttfreie Masse aus BIA-Messung* (wenn kein ADP zur Verfügung stand), oder durch *Größe* (wenn weder ADP noch BIA, also keine Information zur Körperzusammensetzung zur Verfügung stand), die dann 24,7 % bzw. 20,0 % der AEE-Varianz erklärten (in VM-Counts Modellen). Diese Ergebnisse weisen darauf hin, dass mittels Akzelerometrie geeignete Aktivitätsparameter (Einzelachsen-Counts, Raumvektor-Counts) zur Vorhersage von AEE abgeleitet werden können; und, dass durch zusätzliche Informationen zur Körperzusammensetzung (*fettfreie Masse*) oder Anthropometrie (*Größe*) die Vorhersage von AEE signifikant verbessert werden kann. Informationen über KA aus Fragebögen, Kohlenhydrataufnahme, und Ruhepuls können die Varianzerklärung von AEE zusätzlich verbessern, jedoch sollte der Aufwand diese Informationen zu erheben berücksichtigt werden angesichts des begrenzten Verbesserungspotentials.

Die Teilnehmer der ActivE-Studie verbrachten durchschnittlich 130 Minuten pro Tag in KA mit geringer Intensität, 98 Minuten pro Tag in KA mit moderater Intensität, und 21 Minuten pro Tag in KA mit starker Intensität, was 250 Minuten pro Tag in Gesamtaktivität ergibt. Es zeigte sich ein inverser Zusammenhang von AEE, *Zeit in Gesamtaktivität* (unabhängig von Intensität) bzw. *Zeit in KA mit moderater Intensität* (mit und ohne Berücksichtigung der komplementären Intensitätskategorien) mit der Glucose-Konzentration; ein inverser Zusammenhang von *Zeit in*

KA mit starker Intensität bzw. *Zeit-Anteil von KA mit starker Intensität* mit der (log)-CRP-Konzentration; und ein inverser Zusammenhang des (vorhergesagten) AEE mit dem (log)-HOMA-Index. Diese Ergebnisse deuten darauf hin, dass für die Erzielung positiver Effekte bei kardiometabolischen Faktoren im Zusammenhang mit der Glukosehomöostase die Gesamtaktivität unabhängig von der Intensität relevant sein könnte, wobei KA mit moderater Intensität einen vielversprechenden Beitrag leistet; hingegen könnte für Parameter im Zusammenhang mit Entzündungsreaktionen die Intensität der KA eine entscheidende Rolle spielen, wobei hier KA mit starker Intensität einen signifikanten Beitrag leisten könnte.

Die Verbesserung der Abschätzung von KA unter Alltagsbedingungen mittels Akzelerometrie scheint vielversprechend angesichts der fortlaufenden Weiterentwicklung der Technologie und Datenverarbeitung, sowie des Einsatzes von modernen Modellierungsmethoden und Algorithmen, um auch die komplexeren "Roh"-Beschleunigungsdaten zu verarbeiten und zu analysieren. Allgemeingültige Vereinbarungen darüber wie Akzelerometerdaten verarbeitet und welche Daten veröffentlicht werden sollten, würden die Vergleichbarkeit von Studien und die Validität von gepoolten Analysen erhöhen. Letztendlich ermöglicht eine genaue quantitative Beurteilung von KA eine verbesserte Quantifizierung, Charakterisierung und Vorhersage des AEE, sowie eine verbesserte Quantifizierung von Dosis-Wirkungs-Beziehungen und (kausalen) Zusammenhängen zwischen Aktivitätsparametern (einschließlich AEE) und Gesundheitsparametern, was wiederum für die Erstellung von gesundheitsbezogenen Empfehlungen von wesentlicher Bedeutung ist.

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10 Appendix

Table 10-1 Sample size calculation for the ActivE study: Total sample size for different scenarios

	partial correlation r = 0.4	partial correlation r = 0.57
model with 2 predictors	**47**	**22**
model with 4 predictors	**49**	**24**

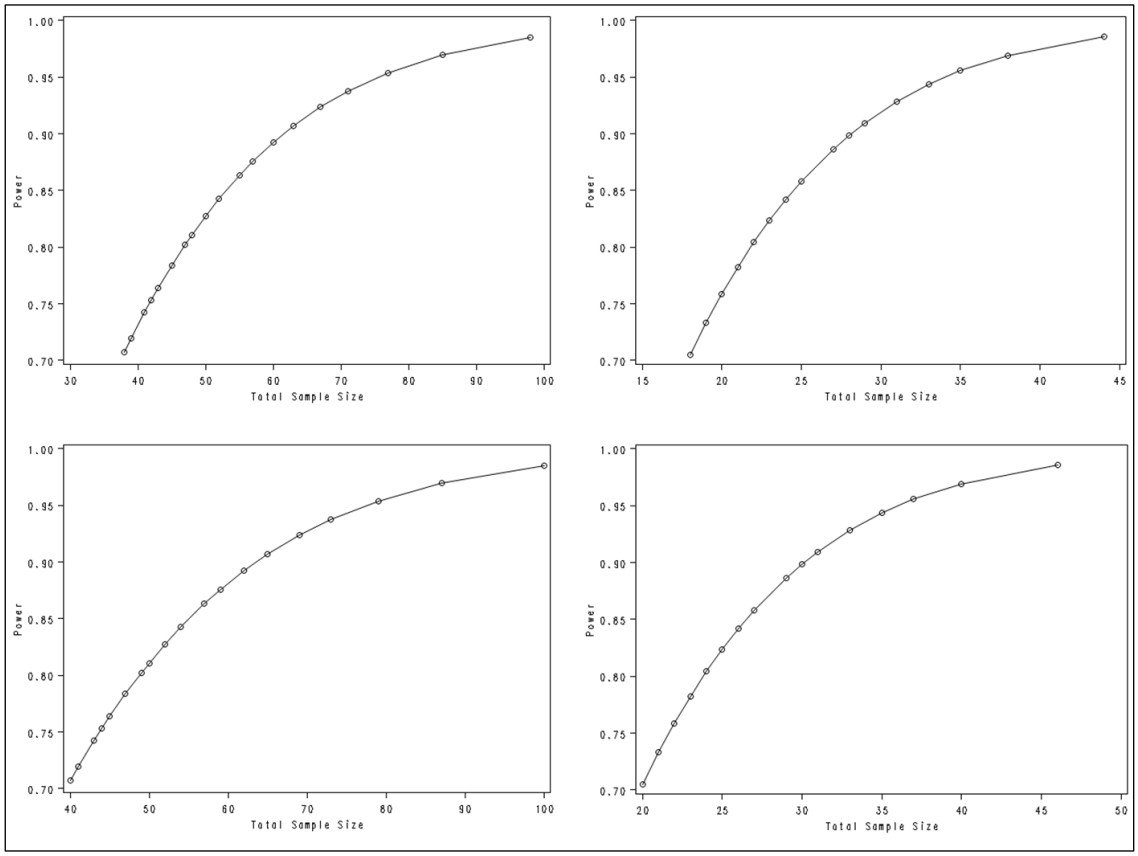

Figure 10-1 Plots of sample size calculation for a given alpha level of 0.05, a power of 0.80 and different scenarios for partial correlation coefficients (r = 0.4 left column, r = 0.57 right column) and number of predictors in the full model (p = 2 top row, p = 4 bottom row)

Sample size calculation was performed using the SAS procedure PROC POWER and the statement option MULTREG, which is intended for Type III F tests of sets of predictors in multiple linear regression, assuming either fixed or normally distributed predictors (default).

IndCal
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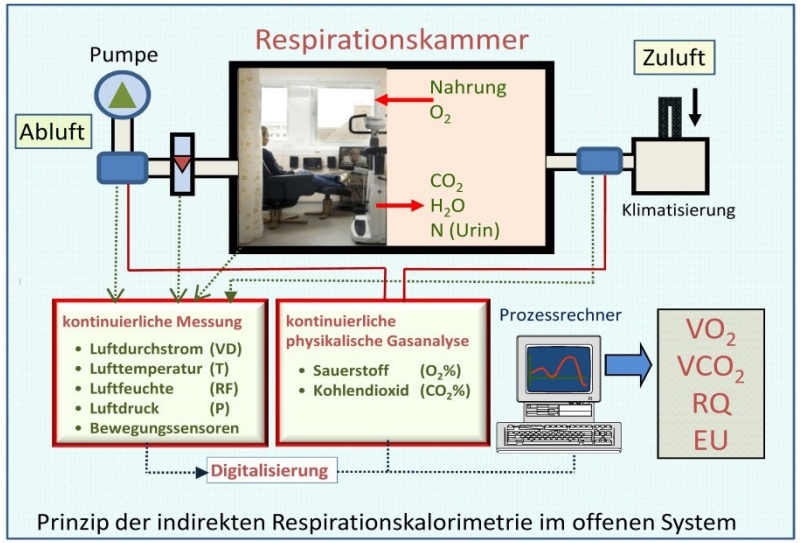
Respirationskammer (Stoffwechselkammer)

FRANZ VOLHARD Clinical Research Center



Prinzip der indirekten Respirationskalorimetrie im offenen System

Berechnungsgrundlagen (Brown, D et al.,1984)

Umrechnung der Luftvolumina auf Standardbedingungen:

STPD = Standard Temperature, Pressure, Dry, (0°C ,760 Torr, 0% RF)

Umrechungsfaktor: $F_{STPD} = f(T, RF, P)$; $VD_{STPD} = VD \times F_{STPD}$, $VL_{STPD} = VL \times F_{STPD}$

Berechnung des Gaswechsels:

Intervalle (IZ): 5, 10, 15, 20 oder 30 min

$$VO_2 = VD_{STPD} \times \sum_{t=0}^{IZ} [O_2\%(F)_t - O_2\%(M)_t)] + VL_{STPD} \times [O_2\%(M)_{IZ} - O_2\%(M)_0]/IZ$$

Technische Daten:

Größe (B/T/H):	200 x 250 x 220 cm (Luftvolumen (VL) brutto 11000 Liter)
Einrichtung:	Relax-Sessel, TV-DVD-Kombination, Radio/CD, Leseleuchte, Beistelltisch, Leseleuchte, Hygiene-Raum, Camping-WC
Patientenüberwachung:	Mini-Farbkamera mit Monitor (ohne Aufzeichnung) Infrarot-Bewegungssensoren (PIR)
Kommunikation:	Telefon
Sensoren:	Durchstrom (100 - 200 l/min), durch Software regelbar Temperatur (15 - 30 °C), durch Software regelbar Rel. Feuchte (0 - 100 %) Luftdruck (600 - 1200 mbar, 450 - 900 Torr) Digitalisierung : ECON, Data Translation Datenübertragung: USB
Gasanalyse:	2 Sensoren in Zuluft (Frischluft) und Abluft (Messluft) CO_2: Infrarotsensor (0- 1 Vol % ± 0,001) O_2: paramagnetischer Sensor (20 - 21 Vol% ± 0,001) Datenübertragung: RS 232 (USB)
Kalibrierung:	softwaregesteuert, 4 Prüfgase

Eichung der gesamten Messanlage durch quantitative Verbrennung von Aceton oder Ethanol (1 g Aceton = 1,542 l O_2; 1,150 l CO_2)

Software:	flexible Programmierung in Visual Basic modular aufgebaut individuell an die speziellen Messaufgaben anpassbar

Konzeption, Planung und Softwareentwicklung:
Dr. Jochen Steiniger, Franz Volhard Centrum für Klinische Forschung am ECRC
Hauptauftragnehmer, Koordination, Prüfgase:
Jörg Steinke, Linde AG, Berlin
Trockenbau, Lüftungstechnik , etc:
Roland Lerchner, ALOS GmbH, Ahrensfelde
Mess-, Steuer- und Regeltechnik:
Steffen Reinicke, digitech gmbh, Ahrensfelde
Gasanalyse-System, Sensoren:
Gunnar M. Baumert, Ulrich Bangert, HTK Hamburg

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MDC MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN BERLIN-BUCH

Figure 10-2 Technical construction of the respiration chamber (in german)

$$EE_i = 15.89 * O_2\ rate_i + 5.07\ CO_2\ rate_i - 4.53\ N\ rate_i\ /\ 1000$$

Where:

EE = energy expenditure of the i-th interval [kJ/min]

O_2 rate = oxygen consumption rate of the i-th interval [ml/min]

CO_2 rate = carbon dioxide production rate of the i-th interval [ml/min]

N rate = nitrogen excretion rate of the i-th interval [mg/min]

Figure 10-3 Modified equation for energy expenditure calculation

The modified equation for energy expenditure calculation based on measurement of oxygen consumption, carbon dioxide production and nitrogen excretion in a respiration chamber setting was developed by Dr. Jochen Steiniger from the Experimental and Clinical Research Center (ECRC)[18] and is derived from established formulas [209, 210], but additionally considers the composition of adipose tissue more appropriately [277].

Comments regarding influence on the results of this thesis:
Using the modified equation for energy expenditure calculation resulted on average in lower REE, and consequently in higher AEE (19 kcal/d for men, 16 kcal/d for women). Concerning the results on predictor selection, in most settings the same predictors were selected with only minimal changes in the value of the regression coefficient estimators. Changes appeared in a very few settings such that the last selected and therefore less contributing predictors were still selected or rather not selected. Concerning the association of AEE and cardiometabolic factors, only minimal changes in the values of the regression coefficients appeared, on average ± 0.02 units. The statistical significance of the results was not affected.

[18] The Experimental and Clinical Research Center (ECRC) is a joint institution of Charité - Universitätsmedizin Berlin and Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin

Table 10-2 Results of NWT (non-wear-time) analysis of accelerometer data using ActiLife software in six participants with detected NWT periods of critical length

Total NWT period [hours:minutes]	**Reason for taking accelerometer off** (information obtained from diary)	**NWT during waking phase**[a] [hours]	**Decision of NWT treatment**
18h22m	delayed change of accelerometer for 2nd week	11h	NWT was considered by deleting that complete day from further calculation
16h39m	showering, forget to put accelerometer on again	7h (3.5h/day)[b]	NWT (per day) not relevant
11h	no reason specified	3h	NWT not relevant
10h57m	forget to put accelerometer on again	2h	NWT not relevant
8h15m	sauna visit	8h	NWT during activity of low intensity (not considered)
7h6m	delayed change of accelerometer for 2nd week	<1h	NWT not relevant

The used NWT algorithm (2 hours of consecutive zeros in *VM counts*, interruptions were not allowed) detected 26 participants without any NWT, 7 participants having NWT during sleeping at night (verified with accelerometer diary), which was not considered as NWT, and 17 participants having NWT during waking hours or during sleeping and waking hours. Of these, NWT of 11 participants[19] amounted to 2 – 3 hours per day, which seemed not relevant in relation to a 24-hour day, so these NWT were not considered. Of the remaining 6 participants –listed in the table– with detected NWT between 7 – 18 hours (after verification with diary), only 1 participant had relevant NWT during waking hours, which was considered by deleting the complete day from the calculation of the accelerometer parameters.

[a] If NWT includes sleeping phase (verified with diary) this time was deducted, because NWT during sleeping was not considered as relevant for PA measurement.

[b] NWT during waking hours was evenly distributed over 2 days (before and after midnight).

NWT non-wear-time.

[19] According to the diary, reasons for NWT were: sauna visits (3 participants), sport with high body contact and taking a shower (2 participants), taking a shower/bath (2 participants), swimming (1 participant), changing clothes without accidentally putting the accelerometer on again (1 participant); and no specified reason (2 participants)

Table 10-3 Diagnostic measures for identifying influential observations in linear regression models using SAS procedure *PROC REG*

Diagnostic measure (name in SAS)	Explanation	Used cutoff
RStudent (jackknife residual)	RStudent is the residual (measured value minus predicted value) divided by its standard error calculated without using the current observation [220, 278]	> | 2 |
Leverage	Leverages measures the distance of an observation from the set of X-variables means and the consequent effect on the estimated regression coefficients. It is the diagonal of the projection matrix or hat matrix. [217, 220, 278]	> 2 p/n
Cook's D (Cook's distance)	Cook's D measures the extent to which all regression coefficients change when the particular observation is deleted. It measures the influence of the observation on the estimated regression coefficients. [217, 278-280]	> 4/n
DFFITS	DFFITS describes the standard influence of an observation on the predicted value. It is a scaled measure of the change in the predicted value when the particular observation is deleted. It is closely related to Cook's D. [220, 278]	> 2 $\sqrt{(p/n)}$
DFBETAS	DFBETAS identify influential observations for each single regression coefficient. It measures the change in each estimated parameter in multiples of its standard error and is calculated by deleting the current observation. [220, 278]	> 2 / $\sqrt{n}$

n = number of observations, p = number of model parameters inclusive intercept.

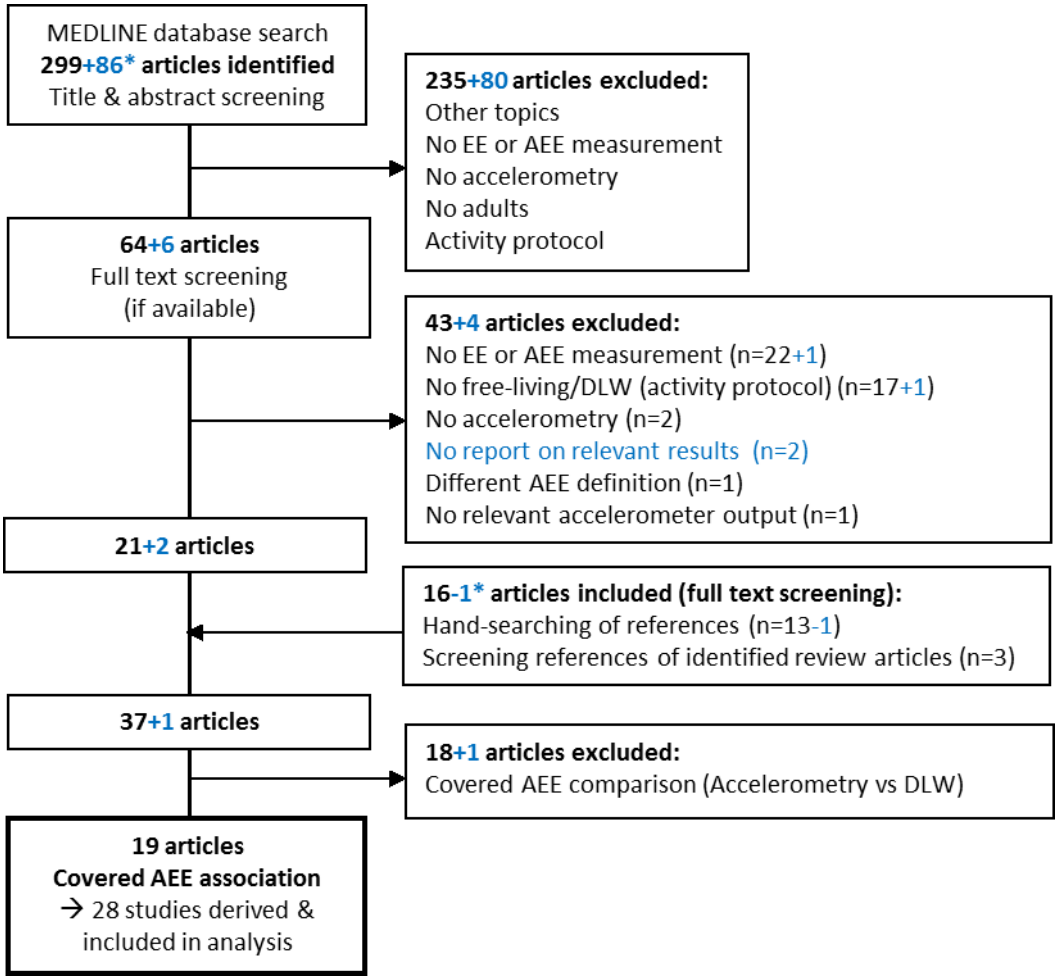

Figure 10-4 Flowchart of article selection of updated literature for the systematic review. Numbers of original search + numbers of updated search (in blue).

The updated literature search was conducted on January 5th 2017 using the publication date 'to 31 December 2016' in the PubMed filter options (see paragraph 4.1.1). Two new articles fulfilled the eligibility criteria after abstract and full text reading, but reported on validation of the accelerometer device by comparing accelerometer-derived AEE and DLW-derived AEE; therefore, they were not considered in the implemented analysis [87, 281].
*One of the two articles [87] was already identified in the original search via reference screening, and in the updated search this article was identified via MEDLINE database search.

AEE activity-related energy expenditure, DLW doubly-labeled water.

Table 10-4 Detailed characteristics of 19 included articles and derived studies considered in systematic review[20]

Reference	**Study population** **Sample size** (n) **Sex** (male/female) **Age** (range or mean ±SD) **BMI or weight** (range or mean ±SD)	**Accelerometer device** **Type of accelerometer** **Body position** **Recording period** **Wear time**	**DLW measurement period** **RMR/BMR/SMR** measurement (method) or calculation (equation) **DIT consideration** **AEE calculation**	**Measured Accelerometer output metric**	**Crude R^2** (Acc-output vs. AEE [*abs*] or AEE per kg [*rel*])[a]
Rabinovich *et al.* (2013) [181]	COPD patients[b] n=40 28 male, 12 female 69 ±5.8 years 27.2 ±4.7 kg/m²	Lifecorder PLUS uniaxial left waist 14 days, waking hours	TEE: DLW (14 days) RMR: IC (hood) DIT: 10% of TEE AEE = TEE-RMR-DIT	Activity score	$_{abs}R^2$=0.20
	COPD patients[b] n=40 29 male, 11 female 69 ±6.1 years 26.8 ±4.8 kg/m²	Actiwatch Spectrum uniaxial left wrist 14 days, waking hours	*See above*	Activity counts	$_{abs}R^2$=0.46
	COPD patients[b] n=39 27 male, 12 female 70 ±5.9 years 25.9 ±5.2 kg/m²	RT3 triaxial right waist 14 days, waking hours	*See above*	VM units	$_{abs}R^2$=0.23
	COPD patients[b] n=40 33 male, 7 female 67 ±6.2 years 27.2 ±4.1 kg/m²	DynaPort Move Monitor triaxial waist, lower back 14 days, waking hours	*See above*	Movement intensity	$_{abs}R^2$=0.49
	COPD patients[b] n=39 32 male, 7 female 69 ±6.6 years 26.8 ±4.5 kg/m²	ActiGraph GT3X triaxial right waist 14 days, waking hours	*See above*	VM units	$_{abs}R^2$=0.46
	COPD patients[b] n=73 58 male, 15 female 68 ±6.4 years 26.4 ±4.5 kg/m²	SenseWear Armband Mini triaxial upper left arm, triceps 14 days, waking hours	*See above*	Steps	$_{abs}R^2$=0.14
Valenti *et al.* (2013) [230]	overweight, obese n=36 11 male, 25 female 41 ±7 years 31.0 ±2.5 kg/m²	TracmorD triaxial lower back 14 days, 24 hours	TEE: DLW (14 days) SMR: IC (chamber) DIT: 10% of TEE AEE = TEE-SMR-DIT	Counts per day	$_{rel}R^2$=0.58
Horner *et al.* (2013) [189]	10 military cohorts participants n=149 108 male, 41 female 20.6 ±3.9 years weight 67.9 ±12.0 kg	3DNX model V3 & V2 triaxial small of the back 7 – 10 days, waking hours	TEE: DLW (7 – 10 days) RMR: calc (Schofield) DIT: 10% of TEE AEE = TEE-RMR-DIT	*Log*-counts per day	R^2=0.07 (vs. log $_{abs}$AEE)
Tudor-Locke *et al.* (2012) [191]	normal- & overweight n=54 20 male, 34 female 20 – 36 years 18.5 – 27.6 kg/m²	Actigraph GT1M uniaxial hip 7 days, waking hours	TEE: DLW (14 days) RMR: IC (hood) DIT: 10% of TEE AEE = TEE-RMR-DIT	Steps per day	$_{abs}R^2$=0.0752

[20] In the framework of this thesis this table has already been published by the author: [233] Jeran S, Steinbrecher A, Pischon T. Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review. International Journal of Obesity 2016; 40: 1187-1197.

Table 10-4 *Continued*

Reference	**Study population** **Sample size** (n) **Sex** (male/female) **Age** (range or mean ±SD) **BMI or weight** (range or mean ±SD)	**Accelerometer device** **Type of accelerometer** **Body position** **Recording period** **Wear time**	**DLW measurement period** **RMR/BMR/SMR** measurement (method) or calculation (equation) **DIT consideration** **AEE calculation**	**Measured Accelerometer output metric**	**Crude R^2** (Acc-output vs. AEE [*abs*] or AEE per kg [*rel*])[a]
Kinnunen *et al.* (2012 [190])	Conscripts n=22 male 19 – 20 years weight 57 – 111 kg	Polar activity recorder uniaxial non-dominant wrist 7 days, 24 hours	TEE: DLW (7 days) BMR: calc (Schofield) DIT: 10% of TEE AEE = TEE-BMR-DIT	Normalized hand movements per min	NS
Skipworth *et al.* (2011) [229]	cancer patients, healthy subjects n=14 12 male, 2 female 25 – 76 years 20.4 – 33.5 kg/m²	ActivPAL uniaxial right thigh 14 days, 24 hours	TEE: DLW (14 days) RMR: IC (hood) AEE = TEE-RMR	Steps per min	$_{rel}R^2$=0.80
van Hees *et al.* (2011)[39]	non-pregnant n=65[c] female 20 – 35 years 27.8 ±6.6 kg/m²	GENEA triaxial right or left wrist 10 days, 24 hours	TEE: DLW (10 days) RMR: IC (hood) DIT: 10% of TEE AEE = TEE-RMR-DIT	VM-acceleration[d]	$_{abs}R^2$=0.21 $_{rel}R^2$=0.27[b] (n=48, >7 days)
	pregnant n=30[c] female 20 – 35 years 27.7 ±5.3 kg/m²	*See above*	*See above*	*See above*	$_{abs}R^2$=0.09 $_{rel}R^2$=0.05[b] (n=26, >7 days)
Colbert *et al.* (2011) [90]	older adults n=56 12 male, 44 female 74.7 ±6.5 years 25.8 ±4.2 kg/m²	Actigraph GT1M uniaxial right waist 10 days, waking hours	TEE: DLW (10 days) RMR: IC (hood) DIT: 10% of TEE AEE = TEE-RMR-DIT	1) Steps per day 2) Counts per day	1) $_{abs}R^2$=0.342 $_{rel}R^2$=0.396 2) $_{abs}R^2$=0.312 $_{rel}R^2$=0.315
	See above	SenseWear Pro3 Armband NS/biaxial[e] NS/upper arm[e] 10 days, waking hours	*See above*	Steps per day	$_{abs}R^2$=0.318 $_{rel}R^2$=0.348
Pomeroy *et al.* (2011) [182]	American Indians n=50 25 male, 25 female 20 – 34 years 30.0 (men), 25.6 (women) kg/m² (median)	ActiGraph MTI (model 7164) uniaxial hip 7 days, waking hours	TEE: DLW (7 days) RMR: IC (hood) DIT: 10% of TEE AEE = TEE-RMR-DIT	Steps per day	NS
	See above	Dynastream AMP-331 triaxial ankle 7 days, waking hours	*See above*	Steps per day	NS
Assah *et al.* (2011) [192]	healthy urban/rural Cameroonians n=33 16 male, 17 female 25 – 50 years 27.1 ±4.6 kg/m²	Actiheart uniaxial + heart rate chest 7 days, 24 hours	TEE: DLW (7 days) RMR: IC (handheld) SMR: calc (= 0.9*RMR) DIT: 10% of TEE AEE = TEE-RMR-SMR-DIT	Acceleration	$_{rel}R^2$=0.29
Bonomi *et al.* (2010) [185]	healthy volunteers n=30 18 male, 12 female 26 – 60 years 19.0 – 31.4 kg/m²	TracmorD triaxial lower back 14 days, waking hours	TEE: DLW (14 days) SMR: IC (chamber) DIT: 10% of TEE AEE = TEE-SMR-DIT	Counts per day	$_{abs}R^2$=0.29 $_{rel}R^2$=0.50

Table 10-4 *Continued*

Reference	**Study population** **Sample size** (n) **Sex** (male/female) **Age** (range or mean ±SD) **BMI or weight** (range or mean ±SD)	**Accelerometer device** **Type of accelerometer** **Body position** **Recording period** **Wear time**	**DLW measurement period** **RMR/BMR/SMR** measurement (method) or calculation (equation) **DIT consideration** **AEE calculation**	**Measured Accelerometer output metric**	**Crude R^2** (Acc-output vs. AEE [*abs*] or AEE per kg [*rel*])[a]
Bonomi *et al.* (2009) [186]	healthy volunteers n=15 9 male, 6 female 26 – 59 years 19.6 – 29.5 kg/m²	Tracmor triaxial lower back 5 days, waking hours	TEE: DLW (14 days) SMR: IC (chamber) DIT: 10% of TEE AEE = TEE-SMR-DIT	Counts per day	NS
Assah *et al.* (2009) [184]	healthy urban/rural Cameroonians n=33 16 male, 17 female 25 – 50 years 27.1 ±4.6 kg/m²	Actigraph GT1M uniaxial waist 7 days, 24 hours	TEE: DLW (7 days) RMR: IC (handheld) SMR: calc (= 0.9*RMR) DIT: 10% of TEE AEE = TEE-RMR-SMR-DIT	Counts per day	$_{rel}R^2$=0.14
Pietiläinen *et al.* (2008) [194]	monozygotic twins (weight discordant) n=20[c] 10 male, 10 female 25.6 ±1.3 years[f] 25.7 ±2.7 kg/m² (non obese), 31.4 ±2.2 kg/m² (obese)[f]	Tracmor triaxial lower back 7 days, waking hours	TEE: DLW (14 days) BMR: IC (hood) DIT: 10% of TEE AEE = TEE-BMR-DIT	Counts per day	$_{abs}R^2$=0.46 $_{rel}R^2$=0.62 (n=10)
Plasqui *et al.* (2005) [188]	healthy twins n=29 10 male, 19 female 24 ±6 years 22.9 ±4.3 kg/m²	Tracmor triaxial lower back 15 days, waking hours	TEE: DLW (14 days) SMR: IC (chamber) DIT: 10% of TEE AEE = TEE-SMR-DIT	VM-counts per day (vertical counts per day)	$_{rel}R^2$=0.60 (NS)
Adams *et al.* (2005) [193]	university & general population n=80[c] female 40 – 65 years 18.7 – 38.2 kg/m²	Actigraph MTI (model 7164) uniaxial NS/trunk[e] 14 days, NS/waking hours[e]	TEE: DLW (14 days) RMR: calc (Arciero) AEE = TEE-RMR	Daily counts per min	$_{rel}R^2$=0.09 (n=72)
Mâsse *et al.* (2004) [187]	healthy African American, Hispanic n=136 female 40.1 – 71.1 years 19.1 – 59.9 kg/m²	CSA (model 7164) uniaxial right hip 7 days, waking hours	TEE: DLW (14 days, second week used) RMR: IC (hood) DIT: 10% of TEE AEE = TEE-RMR-DIT	1) Counts per day 2) Weight adj. counts per day 3) FFM adj. counts per day	1) $_{abs}R^2$=0.043 2) $_{abs}R^2$=0.090 3) $_{abs}R^2$=0.109
Leenders *et al.* (2001) [183]	healthy volunteers n=13 female 21 – 37 years 19.9 – 27.7 kg/m²	Tritrac-R3D triaxial right hip 7 days, waking hours	TEE: DLW (7 days) RMR: IC (hood) DIT: 10% of TEE AEE = TEE-RMR-DIT	1) VM-counts per day 2) Vertical-counts per day	1) $_{abs}R^2$=0.292 2) $_{abs}R^2$=0.27
	See above	CSA (model 7164) uniaxial left hip 7 days, waking hours	*See above*	1) Counts per day 2) Steps per day	1) $_{abs}R^2$=0.203 2) $_{abs}R^2$=0.176
Bouten *et al.* (1996) [195]	healthy volunteers n=30 16 male, 14 female 27.1 ±5.0 years 24.1 ±2.3 kg/m²	Tracmor triaxial lower back 7 days, waking hours	TEE: DLW (14 days, first week used) SMR: IC (chamber) AEE = TEE-SMR	Counts per min[g]	$_{abs}R^2$=0.22 $_{rel}R^2$=0.40

[a] In the model, the dependent AEE variable was considered as absolute [abs] or relative [rel] measure.
[b] Data were obtained from supplement information of the article.
[c] Analytic sample size was different, see crude R^2 column.

[d] Extracted data represent VM-acceleration using imputation with wear time at similar time.
[e] Missing information on Acc type, body position or wear time were substituted as specified after slash (information based on other references using the same device).
[f] SD was calculated from reported standard error (SE) and sample size (SD = SE * √n).
[g] Extracted data represent counts per min corrected for transportation vibrations.

Acc accelerometer, adj. adjusted, AEE activity-related energy expenditure, BMI body mass index, BMR basal metabolic rate, calc calculation, COPD chronic obstructive pulmonary disease, DIT diet-induced thermogenesis, DLW doubly-labeled water, FFM fat-free mass, IC indirect calorimetry, NS not stated, RMR resting metabolic rate, SD standard deviation, SMR sleeping metabolic rate, TEE total energy expenditure, VM vector magnitude.

Table 10-5 Association of accelerometer-derived activity parameters using Spearman rank correlation (n=50)

	VM counts	Axis 1 counts	Axis 2 counts	Axis 3 counts	Steps per day	Time in inactivity	Time in low PA	Time in moderate PA	Time in vigorous PA	Time in MVPA	Time in total activity	Proportion in low PA	Proportion in moderate PA	Proportion in vigorous PA
Spearman's Rank Correlation Coefficients (unadjusted), p-value														
VM counts [cpm]	1.000													
Axis 1 counts [cpm]	0.919	1.000												
	<0.001													
Axis 2 counts [cpm]	0.917	0.808	1.000											
	<0.001	***<0.001***												
Axis 3 counts [cpm]	0.849	0.714	0.654	1.000										
	<0.001	***<0.001***	***<0.001***											
Steps per day	0.900	0.922	0.869	0.668	1.000									
	<0.001	***<0.001***	***<0.001***	***<0.001***										
Time in inactivity [min/d]	-0.916	-0.799	-0.855	-0.805	-0.791	1.000								
	<0.001	***<0.001***	***<0.001***	***<0.001***	***<0.001***									
Time in low PA [min/d]	0.673	0.575	0.641	0.564	0.546	-0.884	1.000							
	<0.001	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***								
Time in moderate PA [min/d]	0.874	0.710	0.828	0.788	0.771	-0.846	0.594	1.000						
	<0.001	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***							
Time in vigorous PA [min/d]	0.763	0.834	0.633	0.660	0.712	-0.568	0.318	0.442	1.000					
	<0.001	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***0.025***	***0.001***						
Time in MVPA [min/d]	0.974	0.860	0.890	0.874	0.877	-0.884	0.603	0.939	0.683	1.000				
	<0.001	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***					
Time in total activity [min/d]	0.916	0.799	0.855	0.805	0.791	-1.000	0.884	0.846	0.568	0.884	1.000			
	<0.001	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***				
Proportion in low PA [%]	-0.343	-0.346	-0.290	-0.341	-0.378	0.012	0.412	-0.400	-0.422	-0.449	-0.012	1.000		
	0.015	***0.014***	***0.041***	***0.015***	***0.007***	*0.933*	***0.003***	***0.004***	***0.002***	***0.001***	*0.933*			
Proportion in moderate PA [%]	0.128	0.021	0.153	0.168	0.156	0.045	-0.367	0.452	-0.092	0.303	-0.045	-0.766	1.000	
	0.374	*0.883*	*0.289*	*0.245*	*0.280*	*0.759*	***0.009***	***<0.001***	*0.524*	***0.033***	*0.759*	***<0.001***		
Proportion in vigorous PA [%]	0.467	0.613	0.336	0.398	0.466	-0.210	-0.028	0.110	0.909	0.383	0.210	-0.464	-0.134	1.000
	<0.001	***<0.001***	***0.017***	***0.004***	***<0.001***	*0.144*	*0.849*	*0.447*	***<0.001***	***0.006***	*0.144*	***<0.001***	*0.352*	

cpm counts per minute, MVPA moderate-to-vigorous physical activity, PA physical activity, VM vector magnitude,

Table 10-6 Association of preselected candidate variables and AEE using Spearman rank correlation (n=49)

	AEE	Axis 1 counts	VM counts	$Locomotion_{QUAP}$	$Sitting_{QUAP}$	$MPA+walking_{IPAQ}$	Height	FFM_{BIA}	FFM_{ADP}	Resting heart rate	HGS_{max}	Carbohydrate intake	Energy intake
Spearman's Rank Correlation Coefficients (unadjusted), p-value													
AEE [kcal/d]	1.000												
Axis 1 counts [cpm]	0.497 ***<0.001***	1.000											
VM counts [cpm]	0.493 ***<0.001***	0.924 ***<0.001***	1.000										
$Locomotion_{QUAP}$ [h/week]	0.354 ***0.013***	0.234 *0.106*	0.320 ***0.025***	1.000									
$Sitting_{QUAP}$ [h/d]	-0.339 ***0.017***	-0.221 *0.128*	-0.189 *0.194*	0.096 *0.513*	1.000								
$MPA+walking_{IPAQ}$ [min/d]	0.329 ***0.021***	0.235 *0.104*	0.331 ***0.020***	0.314 ***0.028***	-0.262 *0.069*	1.000							
Height [cm]	0.515 ***<0.001***	0.038 *0.795*	-0.011 *0.940*	-0.008 *0.958*	-0.065 *0.658*	-0.215 *0.137*	1.000						
FFM_{BIA} [kg]	0.541 ***<0.001***	0.008 *0.956*	-0.036 *0.803*	-0.049 *0.736*	-0.107 *0.464*	-0.118 *0.421*	0.857 ***<0.001***	1.000					
FFM_{ADP} [kg]	0.609 ***<0.001***	0.054 *0.712*	0.007 *0.959*	-0.008 *0.958*	-0.135 *0.356*	-0.142 *0.329*	0.900 ***<0.001***	0.955 ***<0.001***	1.000				
Resting heart rate [bpm]	-0.445 ***0.001***	-0.227 *0.117*	-0.205 *0.157*	-0.120 *0.413*	0.127 *0.384*	0.202 *0.163*	-0.333 ***0.020***	-0.223 *0.123*	-0.362 ***0.011***	1.000			
HGS_{max} [kg]	0.401 ***0.004***	-0.052 *0.721*	-0.094 *0.519*	-0.099 *0.499*	-0.143 *0.327*	-0.145 *0.320*	0.768 ***<0.001***	0.805 ***<0.001***	0.812 ***<0.001***	-0.231 *0.110*	1.000		
Carbohydrate intake [g/d]	0.387 ***0.006***	0.151 *0.300*	0.084 *0.565*	-0.025 *0.867*	0.071 *0.627*	-0.116 *0.427*	0.256 *0.076*	0.206 *0.156*	0.293 ***0.041***	-0.326 ***0.022***	0.181 *0.213*	1.000	
Energy intake [kcal/d]	0.442 ***0.001***	0.277 *0.054*	0.194 *0.183*	-0.093 *0.525*	-0.004 *0.978*	-0.122 *0.402*	0.454 ***0.001***	0.391 ***0.006***	0.458 ***<0.001***	-0.286 ***0.046***	0.377 ***0.008***	0.789 ***<0.001***	1.000
ANOVA / Pearson's Correlation Coefficients (unadjusted), p-value													
Sex	-0.329 ***0.021***	0.105 *0.472*	0.092 *0.530*	0.207 *0.154*	0.189 *0.194*	0.260 *0.071*	-0.732 ***<0.001***	-0.830 ***<0.001***	-0.846 ***<0.001***	0.275 *0.056*	-0.775 ***<0.001***	-0.241 *0.096*	-0.435 ***0.002***

ADP air-displacement plethysmography, AEE activity-related energy expenditure, BIA bioelectrical impedance analysis, cpm counts per minute, FFM fat-free mass, HGS handgrip strength, IPAQ International Physical Activity Questionnaire, MPA moderate physical activity, QUAP questionnaire of physical activity of previous 12 months, VM vector magnitude

Table 10-7 Association of preselected candidate variables and AEE using Partial Spearman rank correlation, adjusted for sex (n=49)

	AEE	Axis 1 counts	VM counts	$Locomotion_{QUAP}$	$Sitting_{QUAP}$	$MPA+walking_{IPAQ}$	Height	FFM_{BIA}	FFM_{ADP}	Resting heart rate	HGS_{max}	Carbohydrate intake	Energy intake
Partial Spearman's Rank Correlation Coefficients (adjusted for sex), p-value													
AEE [kcal/d]	1.000												
Axis 1 counts [cpm]	0.581 ***<0.001***	1.000											
VM counts [cpm]	0.587 ***<0.001***	0.924 ***<0.001***	1.000										
$Locomotion_{QUAP}$ [h/week]	0.480 ***<0.001***	0.215 *0.142*	0.301 ***0.038***	1.000									
$Sitting_{QUAP}$ [h/d]	-0.302 ***0.037***	-0.245 *0.093*	-0.216 *0.140*	0.060 *0.687*	1.000								
$MPA+walking_{IPAQ}$ [min/d]	0.456 ***0.001***	0.216 *0.140*	0.312 ***0.031***	0.276 *0.057*	-0.314 ***0.030***	1.000							
Height [cm]	0.394 ***0.006***	0.188 *0.202*	0.136 *0.357*	0.252 *0.084*	0.097 *0.510*	-0.065 *0.662*	1.000						
FFM_{BIA} [kg]	0.462 ***<0.001***	0.186 *0.205*	0.136 *0.357*	0.258 *0.076*	0.065 *0.663*	0.140 *0.341*	0.631 ***<0.001***	1.000					
FFM_{ADP} [kg]	0.603 ***<0.001***	0.279 *0.055*	0.224 *0.126*	0.348 ***0.015***	0.017 *0.911*	0.100 *0.498*	0.752 ***<0.001***	0.848 ***<0.001***	1.000				
Resting heart rate [bpm]	-0.390 ***0.006***	-0.266 *0.067*	-0.250 *0.087*	-0.189 *0.199*	0.087 *0.554*	0.152 *0.302*	-0.219 *0.135*	-0.016 *0.913*	-0.280 *0.054*	1.000			
HGS_{max} [kg]	0.190 *0.195*	0.075 *0.611*	0.029 *0.842*	0.165 *0.263*	-0.002 *0.988*	0.088 *0.550*	0.389 ***0.006***	0.362 ***0.011***	0.368 ***0.010***	-0.032 *0.831*	1.000		
Carbohydrate intake [g/d]	0.333 ***0.021***	0.184 *0.211*	0.120 *0.417*	0.030 *0.839*	0.116 *0.432*	-0.065 *0.660*	0.123 *0.404*	0.017 *0.907*	0.181 *0.219*	-0.282 *0.052*	-0.028 *0.852*	1.000	
Energy intake [kcal/d]	0.337 ***0.019***	0.366 ***0.011***	0.284 *0.051*	0.007 *0.960*	0.080 *0.587*	-0.023 *0.875*	0.207 *0.159*	0.045 *0.762*	0.177 *0.229*	-0.199 *0.175*	0.019 *0.899*	0.785 ***<0.001***	1.000

ADP air-displacement plethysmography, AEE activity-related energy expenditure, BIA bioelectrical impedance analysis, cpm counts per minute, FFM fat-free mass, HGS handgrip strength, IPAQ International Physical Activity Questionnaire, MPA moderate physical activity, QUAP questionnaire of physical activity of previous 12 months, VM vector magnitude

Table 10-8 Details of prediction models for AEE [kcal/d] derived from stepwise selection regression using accelerometer-derived VM counts and the full or reduced sets of preselected variables (n=49)

Setting Model	Selected predictor	beta	SE	p-value	STbeta	pR^2	R^2	adj.R^2	SBC
full variable set									
Model A	Intercept	-883.32	179.88	<0.001	0.00	.	0.707	0.681	528.89
	VM counts [cpm]	1.16	0.24	<0.001	0.42	0.338			
	FFM_{ADP} [kg]	16.46	2.84	<0.001	0.51	0.267			
	$MPA+walking_{IPAQ}$ [min/d]	2.22	0.69	0.002	0.28	0.064			
	Carbohydrate intake [g/d]	1.00	0.42	0.020	0.21	0.039			
Model B	Intercept	-515.50	226.21	0.028	0.00	.	0.754	0.719	528.06
	VM counts [cpm]	0.85	0.25	0.001	0.31	0.338			
	FFM_{ADP} [kg]	15.05	2.73	<0.001	0.47	0.267			
	$MPA+walking_{IPAQ}$ [min/d]	1.55	0.69	0.029	0.20	0.064			
	Carbohydrate intake [g/d]	1.15	0.39	0.006	0.24	0.039			
	$Sitting_{QUAP}$ [h/d]	-21.63	9.18	0.023	-0.20	0.023			
	$Locomotion_{QUAP}$ [h/week]	11.56	5.69	0.048	0.18	0.024			
no ADP									
Model A	Intercept	-304.02	334.71	0.369	0.00	.	0.717	0.684	531.17
	VM counts [cpm]	1.18	0.24	<0.001	0.43	0.338			
	FFM_{BIA} [kg]	13.83	2.65	<0.001	0.44	0.247			
	Carbohydrate intake [g/d]	1.00	0.42	0.021	0.21	0.047			
	$MPA+walking_{IPAQ}$ [min/d]	2.39	0.70	0.001	0.30	0.056			
	Resting heart rate [bpm]	-7.24	3.45	0.042	-0.19	0.029			
Model B	Intercept	-498.07	232.75	0.038	0.00	.	0.743	0.706	530.35
	VM counts [cpm]	0.97	0.26	<0.001	0.35	0.338			
	FFM_{BIA} [kg]	13.44	2.58	<0.001	0.43	0.247			
	Carbohydrate intake [g/d]	1.33	0.40	0.002	0.28	0.047			
	$MPA+walking_{IPAQ}$ [min/d]	1.29	0.69	0.070	0.16	0.056			
	$Sitting_{QUAP}$ [h/d]	-23.64	9.33	0.015	-0.22	0.029			
	$Locomotion_{QUAP}$ [h/week]	12.08	5.82	0.044	0.19	0.026			
no ADP & BIA									
Model A	Intercept	-2442.23	604.51	<0.001	0.00	.	0.724	0.685	533.73
	VM counts [cpm]	0.83	0.27	0.003	0.30	0.338			
	Height [cm]	15.81	3.33	<0.001	0.43	0.200			
	$MPA+walking_{IPAQ}$ [min/d]	1.73	0.74	0.024	0.22	0.079			
	Carbohydrate intake [g/d]	1.25	0.42	0.004	0.26	0.047			
	$Sitting_{QUAP}$ [h/d]	-24.17	9.66	0.016	-0.22	0.030			
	$Locomotion_{QUAP}$ [h/week]	12.90	6.02	0.038	0.20	0.030			
no QUAP									
Model A	Intercept	-883.32	179.88	<0.001	0.00	.	0.707	0.681	528.89
	VM counts [cpm]	1.16	0.24	<0.001	0.42	0.338			
	FFM_{ADP} [kg]	16.46	2.84	<0.001	0.51	0.267			
	$MPA+walking_{IPAQ}$ [min/d]	2.22	0.69	0.002	0.28	0.064			
	Carbohydrate intake [g/d]	1.00	0.42	0.020	0.21	0.039			

Table 10-8 *Continued*

Setting Model	Selected predictor	beta	SE	p-value	STbeta	pR^2	R^2	adj.R^2	SBC
no IPAQ									
Model A	Intercept	-347.48	223.70	0.128	0.00	.	0.724	0.692	529.81
	VM counts [cpm]	0.90	0.26	0.001	0.33	0.338			
	FFM_{ADP} [kg]	13.72	2.79	<0.001	0.42	0.267			
	$Sitting_{QUAP}$ [h/d]	-27.15	9.27	0.005	-0.25	0.037			
	Carbohydrate intake [g/d]	1.14	0.41	0.008	0.24	0.038			
	$Locomotion_{QUAP}$ [h/week]	15.08	5.73	0.012	0.24	0.044			
no IPAQ & QUAP									
Model A	Intercept	-685.55	195.88	0.001	0.00	.	0.605	0.588	535.78
	VM counts [cpm]	1.46	0.26	<0.001	0.53	0.338			
	FFM_{ADP} [kg]	16.81	3.01	<0.001	0.52	0.267			
Model B	Intercept	-763.66	193.78	<0.001	0.00	.	0.637	0.613	535.50
	VM counts [cpm]	1.37	0.25	<0.001	0.50	0.338			
	FFM_{ADP} [kg]	14.87	3.08	<0.001	0.46	0.267			
	Carbohydrate intake [g/d]	0.91	0.46	0.052	0.19	0.032			
no IPAQ & QUAP & ADP									
Model A	Intercept	-800.80	202.20	<0.001	0.00	.	0.631	0.607	536.28
	VM counts [cpm]	1.49	0.25	<0.001	0.54	0.338			
	FFM_{BIA} [kg]	13.73	2.91	<0.001	0.44	0.247			
	Carbohydrate intake [g/d]	1.08	0.45	0.021	0.23	0.047			
no IPAQ & QUAP & ADP & BIA									
Model A	Intercept	-2453.02	636.57	<0.001	0.00	.	0.580	0.552	542.62
	VM counts [cpm]	1.41	0.27	<0.001	0.51	0.338			
	Height [cm]	14.14	3.76	<0.001	0.38	0.200			
	Carbohydrate intake [g/d]	1.05	0.49	0.038	0.22	0.042			
no Nutrition / no Nutrition & QUAP									
Model A	Intercept	-792.23	184.99	<0.001	0.00	.	0.669	0.646	531.06
	VM counts [cpm]	1.26	0.25	<0.001	0.46	0.338			
	FFM_{ADP} [kg]	18.50	2.85	<0.001	0.57	0.267			
	$MPA+walking_{IPAQ}$ [min/d]	2.12	0.72	0.005	0.27	0.064			
Model B	Intercept	-235.91	342.11	0.494	0.00	.	0.694	0.666	531.04
	VM counts [cpm]	1.14	0.25	<0.001	0.42	0.338			
	FFM_{ADP} [kg]	16.85	2.90	<0.001	0.52	0.267			
	$MPA+walking_{IPAQ}$ [min/d]	2.49	0.73	0.001	0.31	0.064			
	Resting heart rate [bpm]	-6.78	3.55	0.062	-0.18	0.025			
no Nutrition & IPAQ									
Model A	Intercept	-288.06	238.88	0.234	0.00	.	0.675	0.646	533.94
	VM counts [cpm]	1.06	0.27	<0.001	0.39	0.338			
	FFM_{ADP} [kg]	16.16	2.84	<0.001	0.50	0.267			
	$Sitting_{QUAP}$ [h/d]	-24.82	9.90	0.016	-0.23	0.037			
	$Locomotion_{QUAP}$ [h/week]	12.89	6.09	0.040	0.20	0.033			
no Nutrition & IPAQ & QUAP									
Model A	Intercept	-685.55	195.88	0.001	0.00	.	0.605	0.588	535.78
	VM counts [cpm]	1.46	0.26	<0.001	0.53	0.338			
	FFM_{ADP} [kg]	16.81	3.01	<0.001	0.52	0.267			

Table 10-8 *Continued*

Setting Model	Selected predictor	beta	SE	p-value	STbeta	pR²	R²	adj.R²	SBC
no Nutrition & IPAQ & QUAP & ADP									
Model A	Intercept	-686.73	206.45	0.002	0.00	.	0.584	0.566	538.29
	VM counts [cpm]	1.61	0.26	<0.001	0.59	0.338			
	FFM_{BIA} [kg]	15.46	2.96	<0.001	0.50	0.247			
no Nutrition & IPAQ & QUAP & ADP & BIA									
Model A	Intercept	-2672.31	652.01	<0.001	0.00	.	0.538	0.518	543.45
	VM counts [cpm]	1.51	0.28	<0.001	0.55	0.338			
	Height [cm]	16.60	3.72	<0.001	0.45	0.200			
no Nutrition & QUAP & ADP									
Model A	Intercept	-48.35	333.58	0.885	0.00	.	0.679	0.650	533.38
	VM counts [cpm]	1.27	0.25	<0.001	0.46	0.338			
	FFM_{BIA} [kg]	15.06	2.74	<0.001	0.48	0.247			
	$MPA+walking_{IPAQ}$ [min/d]	2.35	0.74	0.003	0.30	0.047			
	Resting heart rate [bpm]	-9.09	3.54	0.014	-0.24	0.048			

In Model A predictors were selected stepwise if p-value <0.05. Model B (if applicable) yielded a lower SBC during a step of the stepwise selection process. adj. adjusted, ADP air-displacement plethysmography beta unstandardized regression coefficient, BIA bioelectrical impedance analysis, bpm beats per minute, cpm counts per minute, FFM fat-free mass IPAQ International Physical Activity Questionnaire, MPA moderate physical activity, QUAP questionnaire of physical activity of previous 12 months, SE standard error of beta, STbeta standardized regression coefficient, pR² partial explained variance of the predictor, R² explained variance of the model, SBC Schwarz Bayesian Criterion, VM vector magnitude.

Table 10-9 Details of prediction models for AEE [kcal/d] derived from stepwise selection regression using accelerometer-derived Axis 1 counts and the full or reduced sets of preselected variables (n=49)

Setting Model	Selected predictor	beta	SE	p-value	STbeta	pR²	R²	adj.R²	SBC
full variable set									
Model A	Intercept	-754.19	171.59	<0.001	0.00	.	0.708	0.681	528.75
	Axis 1 counts [cpm]	1.68	0.34	<0.001	0.42	0.340			
	FFM_{ADP} [kg]	16.74	2.83	<0.001	0.52	0.261			
	$MPA+walking_{IPAQ}$ [min/d]	2.43	0.67	0.001	0.30	0.080			
	Carbohydrate intake [g/d]	0.86	0.42	0.048	0.18	0.028			
no ADP									
Model A	Intercept	-191.77	324.85	0.558	0.00	.	0.717	0.684	531.04
	Axis 1 counts [cpm]	1.73	0.35	<0.001	0.43	0.340			
	FFM_{BIA} [kg]	14.19	2.66	<0.001	0.46	0.246			
	$MPA+walking_{IPAQ}$ [min/d]	2.59	0.69	0.001	0.33	0.063			
	Resting heart rate [bpm]	-7.04	3.45	0.048	-0.19	0.041			
	Carbohydrate intake [g/d]	0.86	0.42	0.049	0.18	0.027			

Table 10-9 *Continued*

Setting Model	Selected predictor	beta	SE	p-value	STbeta	pR²	R²	adj.R²	SBC
no ADP & BIA									
Model A	Intercept	-2923.62	598.71	<0.001	0.00	.	0.665	0.634	535.53
	Axis 1 counts [cpm]	1.69	0.37	<0.001	0.42	0.340			
	Height [cm]	17.52	3.52	<0.001	0.47	0.192			
	$MPA+walking_{IPAQ}$ [min/d]	2.70	0.74	0.001	0.34	0.097			
	Carbohydrate intake [g/d]	0.96	0.45	0.038	0.20	0.035			
Model B	Intercept	-2463.14	630.68	<0.001	0.00	.	0.690	0.654	535.50
	Axis 1 counts [cpm]	1.52	0.37	<0.001	0.38	0.340			
	Height [cm]	16.20	3.49	<0.001	0.44	0.192			
	$MPA+walking_{IPAQ}$ [min/d]	2.36	0.74	0.003	0.30	0.097			
	Carbohydrate intake [g/d]	1.02	0.44	0.024	0.22	0.035			
	$Sitting_{QUAP}$ [h/d]	-18.92	10.00	0.065	-0.17	0.026			
no QUAP									
Model A	Intercept	-754.19	171.59	<0.001	0.00	.	0.708	0.681	528.75
	Axis 1 counts [cpm]	1.68	0.34	<0.001	0.42	0.340			
	FFM_{ADP} [kg]	16.74	2.83	<0.001	0.52	0.261			
	$MPA+walking_{IPAQ}$ [min/d]	2.43	0.67	0.001	0.30	0.080			
	Carbohydrate intake [g/d]	0.86	0.42	0.048	0.18	0.028			
no IPAQ									
Model A	Intercept	-194.88	234.87	0.411	0.00	.	0.637	0.612	535.58
	Axis 1 counts [cpm]	1.88	0.37	<0.001	0.47	0.340			
	FFM_{ADP} [kg]	15.60	2.96	<0.001	0.48	0.261			
	$Sitting_{QUAP}$ [h/d]	-21.70	10.30	0.041	-0.20	0.036			
Model B	Intercept	-209.59	217.96	0.342	0.00	.	0.705	0.671	533.08
	Axis 1 counts [cpm]	1.19	0.41	0.006	0.30	0.340			
	FFM_{ADP} [kg]	13.83	2.88	<0.001	0.43	0.261			
	$Sitting_{QUAP}$ [h/d]	-27.61	9.68	0.007	-0.26	0.036			
	$Locomotion_{QUAP}$ [h/week]	15.06	6.12	0.018	0.24	0.028			
	Carbohydrate intake [g/d]	1.06	0.44	0.019	0.22	0.040			
no IPAQ & QUAP									
Model A	Intercept	-518.94	184.02	0.007	0.00	.	0.601	0.583	536.29
	Axis 1 counts [cpm]	2.10	0.37	<0.001	0.53	0.340			
	FFM_{ADP} [kg]	16.61	3.03	<0.001	0.51	0.261			
no IPAQ & QUAP & ADP									
Model A	Intercept	-520.07	191.33	0.009	0.00	.	0.587	0.569	537.99
	Axis 1 counts [cpm]	2.34	0.38	<0.001	0.59	0.340			
	FFM_{BIA} [kg]	15.46	2.95	<0.001	0.50	0.246			
Model B	Intercept	-613.49	192.07	0.003	0.00	.	0.618	0.593	537.98
	Axis 1 counts [cpm]	2.14	0.38	<0.001	0.54	0.340			
	FFM_{BIA} [kg]	14.01	2.96	<0.001	0.45	0.246			
	Carbohydrate intake [g/d]	0.90	0.47	0.060	0.19	0.032			

Table 10-9 *Continued*

Setting Model	Selected predictor	beta	SE	p-value	STbeta	pR²	R²	adj.R²	SBC
no IPAQ & QUAP & ADP & BIA									
Model A	Intercept	-2455.87	652.23	<0.001	0.00	.	0.533	0.512	544.01
	Axis 1 counts [cpm]	2.17	0.40	<0.001	0.54	0.340			
	Height [cm]	16.28	3.74	<0.001	0.44	0.192			
no Nutrition / no Nutrition & QUAP									
Model A	Intercept	-674.07	172.78	<0.001	0.00	.	0.680	0.659	529.28
	Axis 1 counts [cpm]	1.86	0.35	<0.001	0.47	0.340			
	FFM_{ADP} [kg]	18.44	2.80	<0.001	0.57	0.261			
	$MPA+walking_{IPAQ}$ [min/d]	2.33	0.70	0.002	0.29	0.080			
no Nutrition & IPAQ									
Model A	Intercept	-194.88	234.87	0.411	0.00	.	0.637	0.612	535.58
	Axis 1 counts [cpm]	1.88	0.37	<0.001	0.47	0.340			
	FFM_{ADP} [kg]	15.60	2.96	<0.001	0.48	0.261			
	$Sitting_{QUAP}$ [h/d]	-21.70	10.30	0.041	-0.20	0.036			
Model B	Intercept	-160.32	228.80	0.487	0.00	.	0.665	0.634	535.50
	Axis 1 counts [cpm]	1.50	0.41	0.001	0.38	0.340			
	FFM_{ADP} [kg]	16.03	2.89	<0.001	0.50	0.261			
	$Sitting_{QUAP}$ [h/d]	-24.65	10.12	0.019	-0.23	0.036			
	$Locomotion_{QUAP}$ [h/week]	12.19	6.33	0.061	0.19	0.028			
no Nutrition & IPAQ & QUAP									
Model A	Intercept	-518.94	184.02	0.007	0.00	.	0.601	0.583	536.29
	Axis 1 counts [cpm]	2.10	0.37	<0.001	0.53	0.340			
	FFM_{ADP} [kg]	16.61	3.03	<0.001	0.51	0.261			
no Nutrition & IPAQ & QUAP & ADP									
Model A	Intercept	-520.07	191.33	0.009	0.00	.	0.587	0.569	537.99
	Axis 1 counts [cpm]	2.34	0.38	<0.001	0.59	0.340			
	FFM_{BIA} [kg]	15.46	2.95	<0.001	0.50	0.246			
no Nutrition & IPAQ & QUAP & ADP & BIA									
Model A	Intercept	-2455.87	652.23	<0.001	0.00	.	0.533	0.512	544.01
	Axis 1 counts [cpm]	2.17	0.40	<0.001	0.54	0.340			
	Height [cm]	16.28	3.74	<0.001	0.44	0.192			
no Nutrition & QUAP & ADP									
Model A	Intercept	13.04	319.48	0.968	0.00	.	0.690	0.662	531.63
	Axis 1 counts [cpm]	1.88	0.36	<0.001	0.47	0.340			
	FFM_{BIA} [kg]	15.27	2.69	<0.001	0.49	0.246			
	$MPA+walking_{IPAQ}$ [min/d]	2.54	0.72	0.001	0.32	0.063			
	Resting heart rate [bpm]	-8.46	3.50	0.020	-0.22	0.041			

In Model A predictors were selected stepwise if p-value <0.05. Model B (if applicable) yielded a lower SBC during a step of the stepwise selection process. adj. adjusted, ADP air-displacement plethysmography beta unstandardized regression coefficient, BIA bioelectrical impedance analysis, bpm beats per minute, cpm counts per minute, FFM fat-free mass IPAQ International Physical Activity Questionnaire, MPA moderate physical activity, QUAP questionnaire of physical activity of previous 12 months, SE standard error of beta, STbeta standardized regression coefficient, pR^2 partial explained variance of the predictor, R^2 explained variance of the model, SBC Schwarz Bayesian Criterion, VM vector magnitude.

Table 10-10 Prediction models for AEE [kcal/d] derived from stepwise selection regression using accelerometer-derived PA variable set 1 (including *time in low PA*, *time in moderate PA*, *time in vigorous PA*) and the full and reduced sets of preselected variables (n=49)

Setting Model	Predictor[a]	beta	SE	p-value	STbeta	pR²	R²	adj.R²	SBC
full variable set									
Model A	Intercept	-1080.50	201.83	<0.001	0.00	.	0.740	0.703	530.87
	Time in low PA [min/d]	4.05	1.08	0.001	0.41	0.209			
	Time in moderate PA [min/d]	1.10	1.44	0.451	0.08	0.057			
	Time in vigorous PA [min/d]	0.65	3.06	0.832	0.02	0.095			
	FFM_{ADP} [kg]	18.02	2.87	<0.001	0.56	0.295			
	$Locomotion_{QUAP}$ [h/week]	18.30	5.80	0.003	0.29	0.051			
	Carbohydrate intake [g/d]	0.98	0.42	0.025	0.21	0.034			
no ADP									
Model A	Intercept	-1142.71	207.71	<0.001	0.00	.	0.741	0.704	530.59
	Time in low PA [min/d]	4.45	1.10	<0.001	0.45	0.209			
	Time in moderate PA [min/d]	0.95	1.44	0.512	0.07	0.057			
	Time in vigorous PA [min/d]	1.90	3.03	0.533	0.06	0.095			
	FFM_{BIA} [kg]	17.19	2.72	<0.001	0.55	0.287			
	$Locomotion_{QUAP}$ [h/week]	18.29	5.78	0.003	0.29	0.048			
	Carbohydrate intake [g/d]	1.13	0.41	0.009	0.24	0.046			
no ADP & BIA									
Model A	Intercept	-3043.67	624.17	<0.001	0.00	.	0.669	0.622	542.68
	Time in low PA [min/d]	1.44	1.25	0.256	0.14	0.209			
	Time in moderate PA [min/d]	2.45	1.59	0.132	0.18	0.057			
	Time in vigorous PA [min/d]	6.48	3.13	0.044	0.22	0.095			
	Height [cm]	17.27	3.65	<0.001	0.47	0.212			
	$MPA+walking_{IPAQ}$ [min/d]	2.31	0.81	0.006	0.29	0.058			
	Carbohydrate intake [g/d]	1.04	0.47	0.034	0.22	0.038			
Model B	Intercept	-2591.33	662.87	<0.001	0.00	.	0.724	0.669	541.52
	Time in low PA [min/d]	1.24	1.32	0.352	0.12	0.209			
	Time in moderate PA [min/d]	1.94	1.54	0.216	0.14	0.057			
	Time in vigorous PA [min/d]	3.22	3.23	0.324	0.11	0.095			
	Height [cm]	16.18	3.54	<0.001	0.44	0.212			
	$MPA+walking_{IPAQ}$ [min/d]	1.57	0.81	0.059	0.20	0.058			
	Carbohydrate intake [g/d]	1.26	0.45	0.008	0.26	0.038			
	$Locomotion_{QUAP}$ [h/week]	14.66	6.55	0.031	0.23	0.029			
	$Sitting_{QUAP}$ [h/d]	-20.83	10.68	0.058	-0.19	0.026			
no QUAP									
Model A	Intercept	-1004.16	205.99	<0.001	0.00	.	0.722	0.682	534.09
	Time in low PA [min/d]	2.34	1.17	0.053	0.23	0.209			
	Time in moderate PA [min/d]	2.30	1.46	0.122	0.17	0.057			
	Time in vigorous PA [min/d]	4.48	2.89	0.129	0.15	0.095			
	FFM_{ADP} [kg]	17.36	2.94	<0.001	0.54	0.295			
	$MPA+walking_{IPAQ}$ [min/d]	1.87	0.72	0.013	0.24	0.037			
	Carbohydrate intake [g/d]	0.93	0.44	0.039	0.20	0.030			

Table 10-10 *Continued*

Setting Model	Predictor[a]	beta	SE	p-value	STbeta	pR^2	R^2	adj.R^2	SBC
no IPAQ									
Model B	Intercept	-1080.50	201.83	<0.001	0.00	.	0.740	0.703	530.87
	Time in low PA [min/d]	4.05	1.08	0.001	0.41	0.209			
	Time in moderate PA [min/d]	1.10	1.44	0.451	0.08	0.057			
	Time in vigorous PA [min/d]	0.65	3.06	0.832	0.02	0.095			
	FFM_{ADP} [kg]	18.02	2.87	<0.001	0.56	0.295			
	$Locomotion_{QUAP}$ [h/week]	18.30	5.80	0.003	0.29	0.051			
	Carbohydrate intake [g/d]	0.98	0.42	0.025	0.21	0.034			
no IPAQ & QUAP									
Model A	Intercept	-896.06	218.98	<0.001	0.00	.	0.655	0.624	536.85
	Time in low PA [min/d]	3.75	1.18	0.003	0.38	0.209			
	Time in moderate PA [min/d]	1.56	1.56	0.321	0.11	0.057			
	Time in vigorous PA [min/d]	5.89	3.05	0.060	0.20	0.095			
	FFM_{ADP} [kg]	18.56	3.02	<0.001	0.57	0.295			
no IPAQ & QUAP & ADP									
Model A	Intercept	-1032.86	225.23	<0.001	0.00	.	0.680	0.642	537.18
	Time in low PA [min/d]	3.80	1.18	0.003	0.38	0.209			
	Time in moderate PA [min/d]	1.91	1.55	0.223	0.14	0.057			
	Time in vigorous PA [min/d]	5.77	3.04	0.065	0.20	0.095			
	FFM_{BIA} [kg]	16.04	2.96	<0.001	0.52	0.287			
	Carbohydrate intake [g/d]	0.94	0.45	0.044	0.20	0.032			
no IPAQ & QUAP & ADP & BIA									
Model A	Intercept	-2893.90	670.93	<0.001	0.00	.	0.573	0.534	547.40
	Time in low PA [min/d]	3.04	1.29	0.023	0.30	0.209			
	Time in moderate PA [min/d]	1.68	1.74	0.340	0.12	0.057			
	Time in vigorous PA [min/d]	8.32	3.33	0.016	0.28	0.095			
	Height [cm]	17.52	3.75	<0.001	0.47	0.212			
no Nutrition / no Nutrition & IPAQ									
Model A	Intercept	-975.22	206.61	<0.001	0.00	.	0.706	0.672	532.94
	Time in low PA [min/d]	4.38	1.12	<0.001	0.44	0.209			
	Time in moderate PA [min/d]	0.60	1.50	0.689	0.04	0.057			
	Time in vigorous PA [min/d]	2.61	3.10	0.404	0.09	0.095			
	FFM_{ADP} [kg]	20.01	2.87	<0.001	0.62	0.295			
	$Locomotion_{QUAP}$ [h/week]	16.43	6.03	0.009	0.26	0.051			
no Nutrition & QUAP									
Model A	Intercept	-911.90	209.51	<0.001	0.00	.	0.692	0.656	535.23
	Time in low PA [min/d]	2.81	1.20	0.024	0.28	0.209			
	Time in moderate PA [min/d]	1.72	1.49	0.256	0.13	0.057			
	Time in vigorous PA [min/d]	5.96	2.92	0.047	0.20	0.095			
	FFM_{ADP} [kg]	19.30	2.91	<0.001	0.60	0.295			
	$MPA+walking_{IPAQ}$ [min/d]	1.70	0.75	0.029	0.21	0.037			

.

Table 10-10 *Continued*

Setting Model	Predictor[a]	beta	SE	p-value	STbeta	pR^2	R^2	adj.R^2	SBC
no Nutrition & IPAQ & QUAP									
Model A	Intercept	-896.06	218.98	<0.001	0.00	.	0.655	0.624	536.85
	Time in low PA [min/d]	3.75	1.18	0.003	0.38	0.209			
	Time in moderate PA [min/d]	1.56	1.56	0.321	0.11	0.057			
	Time in vigorous PA [min/d]	5.89	3.05	0.060	0.20	0.095			
	FFM_{ADP} [kg]	18.56	3.02	<0.001	0.57	0.295			
no Nutrition & QUAP & ADP / no Nutrition & IPAQ & QUAP & ADP									
Model A	Intercept	-927.20	227.46	<0.001	0.00	.	0.648	0.616	537.95
	Time in low PA [min/d]	4.19	1.21	0.001	0.42	0.209			
	Time in moderate PA [min/d]	1.34	1.58	0.399	0.10	0.057			
	Time in vigorous PA [min/d]	7.49	3.04	0.018	0.25	0.095			
	FFM_{BIA} [kg]	17.70	2.96	<0.001	0.57	0.287			
no Nutrition & IPAQ & QUAP & ADP & BIA									
Model A	Intercept	-2893.90	670.93	<0.001	0.00	.	0.573	0.534	547.40
	Time in low PA [min/d]	3.04	1.29	0.023	0.30	0.209			
	Time in moderate PA [min/d]	1.68	1.74	0.340	0.12	0.057			
	Time in vigorous PA [min/d]	8.32	3.33	0.016	0.28	0.095			
	Height [cm]	17.52	3.75	<0.001	0.47	0.212			

[a] Accelerometer-derived PA variables (*time in low PA, time in moderate PA, time in vigorous PA*) were forced to be included in the model. In Model A the remaining predictors were selected stepwise if p-value <0.05. Model B (if applicable) yielded a lower SBC during a step of the stepwise selection process.
adj. adjusted, ADP air-displacement plethysmography beta unstandardized regression coefficient, BIA bioelectrical impedance analysis, bpm beats per minute, cpm counts per minute, FFM fat-free mass IPAQ International Physical Activity Questionnaire, MPA moderate physical activity, QUAP questionnaire of physical activity of previous 12 months, SE standard error of beta, STbeta standardized regression coefficient, pR^2 partial explained variance of the predictor, R^2 explained variance of the model, SBC Schwarz Bayesian Criterion, VM vector magnitude

Table 10-11 Prediction models for AEE [kcal/d] derived from stepwise selection regression using accelerometer-derived PA variable set 2 (including *time in total activity*, *proportion in moderate PA*, *proportion in vigorous PA*) and the full and reduced sets of preselected variables (n=49)

Setting Model	Predictor[a]	beta	SE	p-value	STbeta	pR²	R²	adj.R²	SBC
full variable set									
Model A	Intercept	-808.55	288.38	0.008	0.00	.	0.736	0.698	531.68
	Time in total activity [min/d]	2.63	0.49	<0.001	0.46	0.312			
	Proportion in moderate PA [%]	-5.18	5.64	0.363	-0.08	0.003			
	Proportion in vigorous PA [%]	-8.31	8.63	0.341	-0.09	0.037			
	FFM_{ADP} [kg]	17.73	2.88	<0.001	0.55	0.293			
	$Locomotion_{QUAP}$ [h/week]	18.02	5.79	0.003	0.28	0.050			
	Carbohydrate intake [g/d]	1.04	0.41	0.016	0.22	0.039			
no ADP									
Model A	Intercept	-822.43	288.46	0.007	0.00	.	0.736	0.699	531.55
	Time in total activity [min/d]	2.88	0.49	<0.001	0.50	0.312			
	Proportion in moderate PA [%]	-6.91	5.71	0.233	-0.11	0.003			
	Proportion in vigorous PA [%]	-6.43	8.55	0.456	-0.07	0.037			
	FFM_{BIA} [kg]	16.93	2.74	<0.001	0.54	0.281			
	$Locomotion_{QUAP}$ [h/week]	18.20	5.78	0.003	0.28	0.048			
	Carbohydrate intake [g/d]	1.20	0.41	0.005	0.25	0.054			
no ADP & BIA									
Model A	Intercept	-3311.25	639.43	<0.001	0.00	.	0.668	0.620	542.86
	Time in total activity [min/d]	2.30	0.57	<0.001	0.40	0.312			
	Proportion in moderate PA [%]	4.84	6.13	0.435	0.08	0.003			
	Proportion in vigorous PA [%]	11.07	8.88	0.219	0.12	0.037			
	Height [cm]	17.01	3.63	<0.001	0.46	0.206			
	$MPA+walking_{IPAQ}$ [min/d]	2.37	0.80	0.005	0.30	0.064			
	Carbohydrate intake [g/d]	1.11	0.46	0.021	0.23	0.046			
Model B	Intercept	-2744.64	640.32	<0.001	0.00	.	0.726	0.672	541.12
	Time in total activity [min/d]	1.69	0.58	0.006	0.29	0.312			
	Proportion in moderate PA [%]	4.68	6.22	0.456	0.07	0.003			
	Proportion in vigorous PA [%]	4.34	9.17	0.639	0.05	0.037			
	Height [cm]	15.81	3.51	<0.001	0.43	0.206			
	$MPA+walking_{IPAQ}$ [min/d]	1.61	0.80	0.051	0.20	0.064			
	Carbohydrate intake [g/d]	1.30	0.43	0.005	0.27	0.046			
	$Locomotion_{QUAP}$ [h/week]	14.44	6.45	0.031	0.23	0.029			
	$Sitting_{QUAP}$ [h/d]	-22.40	10.73	0.043	-0.21	0.030			
no QUAP									
Model A	Intercept	-1119.39	296.58	<0.001	0.00	.	0.722	0.682	534.18
	Time in total activity [min/d]	2.52	0.52	<0.001	0.44	0.312			
	Proportion in moderate PA [%]	1.65	5.70	0.773	0.03	0.003			
	Proportion in vigorous PA [%]	4.90	8.27	0.556	0.05	0.037			
	FFM_{ADP} [kg]	17.20	2.94	<0.001	0.53	0.293			
	$MPA+walking_{IPAQ}$ [min/d]	1.92	0.72	0.011	0.24	0.041			
	Carbohydrate intake [g/d]	0.97	0.42	0.027	0.21	0.035			

Table 10-11 *Continued*

Setting Model	Predictor[a]	beta	SE	p-value	STbeta	pR^2	R^2	adj.R^2	SBC
no IPAQ									
Model A	Intercept	-808.55	288.38	0.008	0.00	.	0.736	0.698	531.68
	Time in total activity [min/d]	2.63	0.49	<0.001	0.46	0.312			
	Proportion in moderate PA [%]	-5.18	5.64	0.363	-0.08	0.003			
	Proportion in vigorous PA [%]	-8.31	8.63	0.341	-0.09	0.037			
	FFM_{ADP} [kg]	17.73	2.88	<0.001	0.55	0.293			
	$Locomotion_{QUAP}$ [h/week]	18.02	5.79	0.003	0.28	0.050			
	Carbohydrate intake [g/d]	1.04	0.41	0.016	0.22	0.039			
no IPAQ & QUAP									
Model A	Intercept	-853.27	314.91	0.010	0.00	.	0.646	0.614	538.19
	Time in total activity [min/d]	3.15	0.53	<0.001	0.55	0.312			
	Proportion in moderate PA [%]	-2.31	6.14	0.709	-0.04	0.003			
	Proportion in vigorous PA [%]	3.91	8.96	0.665	0.04	0.037			
	FFM_{ADP} [kg]	18.48	3.06	<0.001	0.57	0.293			
Model B	Intercept	-968.46	311.15	0.003	0.00	.	0.674	0.637	537.96
	Time in total activity [min/d]	3.03	0.52	<0.001	0.53	0.312			
	Proportion in moderate PA [%]	-0.94	6.00	0.876	-0.01	0.003			
	Proportion in vigorous PA [%]	1.90	8.76	0.829	0.02	0.037			
	FFM_{ADP} [kg]	16.56	3.13	<0.001	0.51	0.293			
	Carbohydrate intake [g/d]	0.88	0.45	0.059	0.18	0.029			
no IPAQ & QUAP & ADP									
Model A	Intercept	-981.93	311.99	0.003	0.00	.	0.674	0.636	538.03
	Time in total activity [min/d]	3.27	0.52	<0.001	0.57	0.312			
	Proportion in moderate PA [%]	-2.50	6.08	0.683	-0.04	0.003			
	Proportion in vigorous PA [%]	3.77	8.69	0.667	0.04	0.037			
	FFM_{BIA} [kg]	15.76	2.98	<0.001	0.51	0.281			
	Carbohydrate intake [g/d]	1.02	0.44	0.026	0.22	0.041			
no IPAQ & QUAP & ADP & BIA									
Model A	Intercept	-2805.07	668.91	<0.001	0.00	.	0.599	0.552	548.20
	Time in total activity [min/d]	2.93	0.57	<0.001	0.51	0.312			
	Proportion in moderate PA [%]	2.03	6.58	0.759	0.03	0.003			
	Proportion in vigorous PA [%]	7.57	9.56	0.433	0.08	0.037			
	Height [cm]	14.76	3.86	<0.001	0.40	0.206			
	Carbohydrate intake [g/d]	1.04	0.50	0.043	0.22	0.040			
no Nutrition / no Nutrition & IPAQ									
Model A	Intercept	-690.32	301.34	0.027	0.00	.	0.696	0.661	534.58
	Time in total activity [min/d]	2.81	0.51	<0.001	0.49	0.312			
	Proportion in moderate PA [%]	-6.35	5.95	0.292	-0.10	0.003			
	Proportion in vigorous PA [%]	-4.94	9.03	0.587	-0.05	0.037			
	FFM_{ADP} [kg]	19.85	2.91	<0.001	0.61	0.293			
	$Locomotion_{QUAP}$ [h/week]	16.22	6.08	0.011	0.25	0.050			

Table 10-11 *Continued*

Setting Model	Predictor[a]	beta	SE	p-value	STbeta	pR²	R²	adj.R²	SBC
no Nutrition & QUAP									
Model A	Intercept	-981.15	304.50	0.002	0.00	.	0.687	0.650	536.09
	Time in total activity [min/d]	2.69	0.54	<0.001	0.47	0.312			
	Proportion in moderate PA [%]	-0.04	5.92	0.994	-0.00	0.003			
	Proportion in vigorous PA [%]	6.90	8.62	0.428	0.07	0.037			
	FFM_{ADP} [kg]	19.27	2.93	<0.001	0.60	0.293			
	$MPA+walking_{IPAQ}$ [min/d]	1.78	0.75	0.023	0.22	0.041			
no Nutrition & IPAQ & QUAP									
Model A	Intercept	-853.27	314.91	0.010	0.00	.	0.646	0.614	538.19
	Time in total activity [min/d]	3.15	0.53	<0.001	0.55	0.312			
	Proportion in moderate PA [%]	-2.31	6.14	0.709	-0.04	0.003			
	Proportion in vigorous PA [%]	3.91	8.96	0.665	0.04	0.037			
	FFM_{ADP} [kg]	18.48	3.06	<0.001	0.57	0.293			
no Nutrition & IPAQ & QUAP & ADP									
Model A	Intercept	-833.32	320.02	0.013	0.00	.	0.633	0.600	539.88
	Time in total activity [min/d]	3.44	0.54	<0.001	0.60	0.312			
	Proportion in moderate PA [%]	-4.11	6.33	0.520	-0.06	0.003			
	Proportion in vigorous PA [%]	6.70	9.01	0.461	0.07	0.037			
	FFM_{BIA} [kg]	17.54	3.02	<0.001	0.56	0.281			
no Nutrition & IPAQ & QUAP & ADP & BIA									
Model A	Intercept	-2986.88	687.89	<0.001	0.00	.	0.558	0.518	549.02
	Time in total activity [min/d]	3.07	0.59	<0.001	0.53	0.312			
	Proportion in moderate PA [%]	0.66	6.79	0.923	0.01	0.003			
	Proportion in vigorous PA [%]	10.63	9.79	0.284	0.12	0.037			
	Height [cm]	17.23	3.81	<0.001	0.47	0.206			
no Nutrition & QUAP & ADP									
Model A	Intercept	-833.32	320.02	0.013	0.00	.	0.633	0.600	539.88
	Time in total activity [min/d]	3.44	0.54	<0.001	0.60	0.312			
	Proportion in moderate PA [%]	-4.11	6.33	0.520	-0.06	0.003			
	Proportion in vigorous PA [%]	6.70	9.01	0.461	0.07	0.037			
	FFM_{BIA} [kg]	17.54	3.02	<0.001	0.56	0.281			
Model B	Intercept	-362.79	388.27	0.355	0.00	.	0.696	0.653	538.50
	Time in total activity [min/d]	2.73	0.56	<0.001	0.48	0.312			
	Proportion in moderate PA [%]	1.50	6.21	0.810	0.02	0.003			
	Proportion in vigorous PA [%]	8.14	8.54	0.346	0.09	0.037			
	FFM_{BIA} [kg]	15.94	2.93	<0.001	0.51	0.281			
	$MPA+walking_{IPAQ}$ [min/d]	2.01	0.79	0.015	0.25	0.025			
	Resting heart rate [bpm]	-8.43	3.70	0.028	-0.22	0.038			

[a] Accelerometer-derived PA variables (*time in total activity, proportion in moderate PA, proportion in vigorous PA*) were forced to be included in the model. In Model A the remaining predictors were selected stepwise if p-value <0.05. Model B (if applicable) yielded a lower SBC during a step of the stepwise selection process. adj. adjusted, ADP air-displacement plethysmography beta unstandardized regression coefficient, BIA bioelectrical impedance analysis, bpm beats per minute, cpm counts per minute, FFM fat-free mass IPAQ International Physical Activity Questionnaire, MPA moderate physical activity, QUAP questionnaire of physical activity of previous 12 months, SE standard error of beta, STbeta standardized regression coefficient, pR^2 partial explained variance of the predictor, R^2 explained variance of the model, SBC Schwarz Bayesian Criterion, VM vector magnitude.

Table 10-12 Recalculated AEE prediction models after exclusion of influential observations using accelerometer-derived VM counts in full and reduced variable sets

AEE prediction models	**Selected predictor variables** Unstandardized Beta (Standard Error), Partial R^2, *p-value*									**Model fit**	
										R^2	adj.R^2
Variable sets	**n**	**VM counts** [cpm]	**FFM_{ADP}** [kg]	**FFM_{BIA}** [kg]	**Height** [cm]	**MPA+walking** $_{IPAQ}$ [min/d]	**Locomotion** $_{QUAP}$ [h/week]	**Sitting** $_{QUAP}$ [h/d]	**Carbohydrate intake** [g/d]	**Resting heart rate** [bpm]	[%]	[%]
Full variable set	45	0.85 (0.24)	15.33 (2.70)			2.92 (0.74)			1.44 (0.43)		73.1	70.5
- Model A		26.1 %	30.5 %			9.0 %			7.5 %			
		0.001	*<0.001*			*<0.001*			*0.002*			
Full variable set	45	0.54 (0.24)	15.04 (2.73)			1.38 (0.74)	16.21 (5.60)	-31.22 (8.65)	1.32 (0.35)		82.0	79.2
- Model B		32.2 %	30.2 %			5.9 %	4.0 %	5.0 %	4.8 %			
		0.033	*<0.001*			*0.071*	*0.006*	*0.001*	*<0.001*			
no ADP	44	1.18 (0.28)		12.18 (2.68)		2.87 (0.85)			1.25 (0.45)	-2.86 (4.08)	74.7	71.4
- Model A		45.8 %		17.8 %		7.3 %			3.5 %	0.3 %		
		<0.001		*<0.001*		*0.002*			*0.009*	*0.488*		
no ADP	44	0.70 (0.26)		13.39 (2.31)		1.07 (0.78)	15.66 (5.87)	-35.29 (9.10)	1.76 (0.39)		79.7	76.4
- Model B		29.6 %		26.4 %		5.7 %	3.9 %	7.1 %	7.1 %			
		0.010		*<0.001*		*0.176*	*0.011*	*<0.001*	*<0.001*			
no ADP & BIA	44	0.54 (0.26)			16.32 (2.92)	1.68 (0.80)	16.27 (5.97)	-36.18 (9.23)	1.71 (0.40)		79.0	75.6
- Model A		29.6 %			21.5 %	9.1 %	4.2 %	7.5 %	7.2 %			
		0.043			*<0.001*	*0.043*	*0.010*	*<0.001*	*<0.001*			
no QUAP	45	0.85 (0.24)	15.33 (2.70)			2.92 (0.74)			1.44 (0.43)		73.1	70.5
- Model A		26.1 %	30.5 %			9.0 %			7.5 %			
		0.001	*<0.001*			*<0.001*			*0.002*			
no IPAQ	44	0.70 (0.23)	15.40 (2.43)				19.77 (5.22)	-32.09 (8.90)	1.42 (0.43)		78.6	75.8
- Model A		26.9 %	35.6 %				8.1 %	3.3 %	4.8 %			
		0.005	*<0.001*				*0.001*	*0.001*	*0.002*			
no IPAQ & QUAP	46	1.26 (0.25)	19.10 (2.73)								65.9	64.3
- Model A		27.1 %	38.8 %									
		<0.001	*<0.001*									
no IPAQ & QUAP	46	1.14 (0.25)	16.89 (2.94)						0.80 (0.50)		63.2	60.5
- Model B		24.0 %	37.0 %						2.2 %			
		<0.001	*<0.001*						*0.119*			
no IPAQ & QUAP	44	1.52 (0.26)		16.27 (2.74)					0.76 (0.49)		66.2	63.7
& ADP		28.8 %		35.4 %					2.1 %			
- Model A		*<0.001*		*<0.001*					*0.127*			
no IPAQ & QUAP	47	1.34 (0.28)			16.46 (3.85)				0.95 (0.56)		55.0	51.9
& ADP & BIA		27.0 %			25.0 %				3.0 %			
- Model A		*<0.001*			*<0.001*				*0.100*			

Table 10-12 *Continued*

AEE prediction models	Selected predictor variables Unstandardized Beta (Standard Error), Partial R^2, *p-value*										Model fit	
	n	VM counts	FFM_{ADP}	FFM_{BIA}	Height	MPA+walking	Locomotion	Sitting	Carbohydrate intake	Resting heart rate	R^2	adj.R^2
Variable sets		[cpm]	[kg]	[kg]	[cm]	$_{IPAQ}$ [min/d]	$_{QUAP}$ [h/week]	$_{QUAP}$ [h/d]	[g/d]	[bpm]	[%]	[%]
no Nutrition	44	1.17 (0.25)	19.34 (2.52)			2.15 (0.73)					73.1	71.1
- Model A		30.0 %	37.3 %			5.8 %						
		<0.001	*<0.001*			*0.006*						
no Nutrition	44	1.10 (0.26)	18.60 (2.64)			2.35 (0.77)				-3.23 (3.42)	73.7	71.0
- Model B		30.0 %	37.3 %			5.8 %				0.6 %		
		<0.001	*<0.001*			*0.004*				*0.350*		
no Nutrition & QUAP	44	1.17 (0.25)	19.34 (2.52)			2.15 (0.73)					73.1	71.1
- Model A		30.0 %	37.3 %			5.8 %						
		<0.001	*<0.001*			*0.006*						
no Nutrition & QUAP	44	1.10 (0.26)	18.60 (2.64)			2.35 (0.77)				-3.23 (3.42)	73.7	71.0
- Model B		30.0 %	37.3 %			5.8 %				0.6 %		
		<0.001	*<0.001*			*0.004*				*0.350*		
no Nutrition & IPAQ	44	0.95 (0.25)	18.53 (2.45)				15.54 (5.61)	-25.79 (9.10)			76.4	74.0
- Model A		30.4 %	37.1 %				4.6 %	4.3 %				
		<0.001	*<0.001*				*0.009*	*0.007*				
no Nutrition & IPAQ	46	1.26 (0.25)	19.10 (2.73)								65.9	64.3
& QUAP		27.1 %	38.8 %									
- Model A		*<0.001*	*<0.001*									
no Nutrition & IPAQ	45	1.38 (0.27)		18.63 (2.90)							64.1	62.4
& QUAP & ADP		28.8		35.3 %								
- Model A		*<0.001*		*<0.001*								
no Nutrition & IPAQ	44	1.67 (0.30)			19.72 (3.79)						56.4	54.3
& QUAP & ADP		27.6 %			28.8 %							
& BIA - Model A		*<0.001*			*<0.001*							
no Nutrition	45	1.38 (0.27)		16.41 (2.62)		2.26 (0.82)				-5.25 (3.57)	71.2	68.3
& QUAP & ADP		33.3 %		32.0 %		4.2 %				1.6 %		
- Model A		*<0.001*		*<0.001*		*0.009*				*0.150*		

Influential observations were excluded individually for each model (paragraph 4.3.4.4). n underlying sample size of the model.

Table 10-13 Recalculated AEE prediction models after exclusion of influential observations using accelerometer-derived Axis 1 counts in full and reduced variable sets

AEE prediction models	**Selected predictor variables** Unstandardized Beta (Standard Error), Partial R^2, *p-value*										**Model fit**	
Variable sets	**n**	**Axis 1 counts** [cpm]	**FFM_{ADP}** [kg]	**FFM_{BIA}** [kg]	**Height** [cm]	**MPA+walking** $_{IPAQ}$ [min/d]	**Locomotion** $_{QUAP}$ [h/week]	**Sitting** $_{QUAP}$ [h/d]	**Carbohydrate intake** [g/d]	**Resting heart rate** [bpm]	R^2 [%]	adj.R^2 [%]
Full variable set	43	1.36 (0.38)	15.72 (2.73)			2.85 (0.75)			1.15 (0.47)		71.9	68.9
- Model A		25.7 %	33.5 %			8.3 %			4.4 %			
		0.001	*<0.001*			*<0.001*			*0.019*			
no ADP	43	1.94 (0.43)		12.25 (2.65)		2.87 (0.82)			0.98 (0.47)	-2.60 (4.06)	76.5	73.3
- Model A		52.2 %		15.5 %		5.0 %			2.7 %	1.1 %		
		<0.001		*<0.001*		*0.001*			*0.045*	*0.527*		
no ADP & BIA	44	1.53 (0.43)			16.26 (3.68)	3.38 (0.85)			1.28 (0.53)		65.7	62.1
- Model A		28.2 %			20.9 %	11.3 %			5.2 %			
		0.001			*<0.001*	*<0.001*			*0.020*			
no ADP & BIA	46	1.36 (0.41)			16.29 (3.29)	3.08 (0.78)		-24.44 (9.80)	1.31 (0.45)		73.0	69.6
- Model B		35.4 %			18.3 %	10.7 %		4.2 %	4.4 %			
		0.002			*<0.001*	*<0.001*		*0.017*	*0.006*			
no QUAP	43	1.36 (0.38)	15.72 (2.73)			2.85 (0.75)			1.15 (0.47)		71.9	68.9
- Model A		25.7 %	33.5 %			8.3 %			4.4 %			
		0.001	*<0.001*			*<0.001*			*0.019*			
no IPAQ	44	1.43 (0.43)	17.30 (2.72)					-25.08 (10.52)			68.0	65.6
- Model A		27.6 %	35.9 %					4.5 %				
		0.002	*<0.001*					*0.022*				
no IPAQ	45	1.16 (0.39)	14.85 (2.38)				18.84 (5.61)	-29.25 (8.66)	1.13 (0.37)		80.6	78.2
- Model B		43.3 %	25.8 %				4.0 %	2.8 %	4.7 %			
		0.004	*<0.001*				*0.002*	*0.002*	*0.004*			
no IPAQ & QUAP	46	1.90 (0.39)	17.56 (2.78)								64.9	63.2
- Model A		32.4 %	32.5 %									
		<0.001	*<0.001*									
no IPAQ & QUAP	47	2.33 (0.41)		15.52 (2.87)							60.8	59.0
& ADP		34.6 %		26.2 %								
- Model A		*<0.001*		*<0.001*								
no IPAQ & QUAP	45	2.09 (0.41)		15.16 (2.84)					0.87 (0.51)		62.4	59.6
& ADP		28.6 %		31.1 %					2.7 %			
- Model B		*<0.001*		*<0.001*					*0.095*			
no IPAQ & QUAP	46	2.21 (0.45)			17.23 (3.81)						53.2	51.1
& ADP & BIA		31.0 %			22.3 %							
- Model A		*<0.001*			*<0.001*							

Table 10-13 *Continued*

AEE prediction models	Selected predictor variables Unstandardized Beta (Standard Error), Partial R^2, *p-value*										Model fit	
	n	Axis 1	FFM_{ADP}	FFM_{BIA}	Height	MPA+walking	Locomotion	Sitting	Carbohydrate	Resting heart	R^2	adj.R^2
Variable sets		**counts** [cpm]	[kg]	[kg]	[cm]	$_{IPAQ}$ [min/d]	$_{QUAP}$ [h/week]	$_{QUAP}$ [h/d]	**intake** [g/d]	**rate** [bpm]	[%]	[%]
no Nutrition	45	1.61 (0.38)	18.62 (2.63)			2.27 (0.75)					70.4	68.2
- Model A		30.7 %	33.1 %			6.6 %						
		<0.001	*<0.001*			*0.004*						
no Nutrition & QUAP	45	1.61 (0.38)	18.62 (2.63)			2.27 (0.75)					70.4	68.2
- Model A		30.7 %	33.1 %			6.6 %						
		<0.001	*<0.001*			*0.004*						
no Nutrition & IPAQ	44	1.43 (0.43)	17.30 (2.72)					-25.08 (10.52)			68.0	65.6
- Model A		27.6 %	35.9 %					4.5 %				
		0.002	*<0.001*					*0.022*				
no Nutrition & IPAQ	45	1.61 (0.39)	16.76 (2.53)				15.66 (6.07)	-23.54 (9.32)			75.9	73.5
- Model B		43.3 %	25.8 %				4.0 %	2.8 %				
		<0.001	*<0.001*				*0.014*	*0.016*				
no Nutrition & IPAQ & QUAP	46	1.90 (0.39)	17.56 (2.78)								64.9	63.2
- Model A		32.4 %	32.5 %									
		<0.001	*<0.001*									
no Nutrition & IPAQ & QUAP & ADP	47	2.33 (0.41)		15.52 (2.87)							60.8	59.0
- Model A		34.6 %		26.2 %								
		<0.001		*<0.001*								
no Nutrition & IPAQ & QUAP & ADP & BIA - Model A	46	2.21 (0.45)			17.23 (3.81)						53.2	51.1
		31.0 %			22.3 %							
		<0.001			*<0.001*							
no Nutrition & QUAP & ADP	44	2.15 (0.41)		13.41 (2.49)		2.46 (0.79)				-5.31 (3.83)	73.4	70.6
- Model A		46.4 %		20.3 %		5.4 %				1.3 %		
		<0.001		*<0.001*		*0.003*				*0.173*		

Influential observations were excluded individually for each model (paragraph 4.3.4.4). n underlying sample size of the model.

Table 10-14 Overview of selected predictor variables when forward selection was used for AEE prediction model recalculation, considering Vector Magnitude counts or Axis 1 counts as accelerometer-derived activity parameter in full and reduced variable sets (n=49)

Variable selection method: ***Forward selection***	**VM counts [cpm]**	FFM_{ADP} [kg]	FFM_{BIA} [kg]	Height [cm]	$MPA+walking_{IPAQ}$ [min/d]	$Locomotion_{QUAP}$ [h/week]	$Sitting_{QUAP}$ [h/d]	Carbohydrate intake [g/d]	Energy intake [kcal/d]	Resting heart rate [bpm]	HGS_{max} [kg]	Sex (male=0, female=1)	**Axis 1 counts [cpm]**	FFM_{ADP} [kg]	FFM_{BIA} [kg]	Height [cm]	$MPA+walking_{IPAQ}$ [min/d]	$Locomotion_{QUAP}$ [h/week]	$Sitting_{QUAP}$ [h/d]	Carbohydrate intake [g/d]	Energy intake [kcal/d]	Resting heart rate [bpm]	HGS_{max} [kg]	Sex (male=0, female=1)
Variable sets																								
Full variable set	✓	✓			✓			✓					✓	✓			✓			✓				
No ADP	✓		✓		✓			✓		✓			✓		✓		✓			✓		✓		
No ADP & BIA	✓			✓	✓	✓	✓	✓					✓			✓	✓			✓				
No QUAP	✓	✓			✓			✓					✓	✓			✓			✓				
No IPAQ	✓	✓				✓	✓	✓					✓	✓					✓					
No IPAQ & QUAP	✓	✓											✓	✓										
No IPAQ & QUAP & ADP	✓		✓					✓					✓		✓									
No IPAQ & QUAP & ADP & BIA	✓			✓				✓					✓			✓								
No Nutrition	✓	✓			✓								✓	✓			✓							
No Nutrition & QUAP	✓	✓			✓								✓	✓			✓							
No Nutrition & IPAQ	✓	✓				✓	✓						✓	✓					✓					
No Nutrition & IPAQ & QUAP	✓	✓											✓	✓										
No Nutrition & IPAQ & QUAP & ADP	✓		✓										✓		✓									
No Nutrition & IPAQ & QUAP & ADP & BIA	✓			✓									✓			✓								
No Nutrition & QUAP & ADP	✓		✓		✓					✓			✓		✓		✓					✓		

Forward selection used p-value limits of 0.05 for the corresponding partial F-statistic for including variables in the model

Table 10-15 Overview of selected predictor variables when backward elimination was used for AEE prediction model recalculation, considering Vector Magnitude counts or Axis 1 counts as accelerometer-derived activity parameter in full and reduced variable sets (n=49)

Variable selection method: ***Backward elimination***	**VM counts [cpm]**	FFM_{ADP} [kg]	FFM_{BIA} [kg]	Height [cm]	$MPA+walking_{IPAQ}$ [min/d]	$Locomotion_{QUAP}$ [h/week]	$Sitting_{QUAP}$ [h/d]	Carbohydrate intake [g/d]	Energy intake [kcal/d]	Resting heart rate [bpm]	HGS_{max} [kg]	Sex (male=0, female=1)	**Axis 1 counts [cpm]**	FFM_{ADP} [kg]	FFM_{BIA} [kg]	Height [cm]	$MPA+walking_{IPAQ}$ [min/d]	$Locomotion_{QUAP}$ [h/week]	$Sitting_{QUAP}$ [h/d]	Carbohydrate intake [g/d]	Energy intake [kcal/d]	Resting heart rate [bpm]	HGS_{max} [kg]	Sex (male=0, female=1)
Variable sets																								
Full variable set	✓	✓			✓	✓	✓	✓					✓	✓			✓			✓				
No ADP	✓		✓			✓	✓	✓					✓		✓		✓			✓		✓		
No ADP & BIA	✓			✓	✓	✓	✓	✓					✓			✓	✓			✓				
No QUAP	✓	✓			✓			✓					✓	✓			✓			✓				
No IPAQ	✓	✓				✓	✓	✓					✓	✓				✓	✓	✓				
No IPAQ & QUAP	✓	✓											✓	✓										
No IPAQ & QUAP & ADP	✓		✓					✓					✓		✓									
No IPAQ & QUAP & ADP & BIA	✓			✓				✓					✓			✓								
No Nutrition	✓	✓			✓								✓	✓			✓							
No Nutrition & QUAP	✓	✓			✓								✓	✓			✓							
No Nutrition & IPAQ	✓	✓				✓	✓						✓	✓					✓					
No Nutrition & IPAQ & QUAP	✓	✓											✓	✓										
No Nutrition & IPAQ & QUAP & ADP	✓		✓										✓		✓									
No Nutrition & IPAQ & QUAP & ADP & BIA	✓			✓									✓			✓								
No Nutrition & QUAP & ADP	✓		✓		✓					✓			✓		✓		✓					✓		

Backward elimination used p-value limits of 0.05 for the corresponding partial F-statistic for retaining variables in the model

Table 10-16 Overview of selected predictor variables when LASSO with optimized SBC was used for AEE prediction model recalculation, considering Vector Magnitude counts or Axis 1 counts as accelerometer-derived activity parameter in full and reduced variable sets (n=49)

Variable selection method: ***LASSO (with SBC)***	**VM counts [cpm]**	FFM_{ADP} [kg]	FFM_{BIA} [kg]	Height [cm]	$MPA+walking_{IPAQ}$ [min/d]	$Locomotion_{QUAP}$ [h/week]	$Sitting_{QUAP}$ [h/d]	Carbohydrate intake [g/d]	Energy intake [kcal/d]	Resting heart rate [bpm]	HGS_{max} [kg]	Sex (male=0, female=1)	**Axis 1 counts [cpm]**	FFM_{ADP} [kg]	FFM_{BIA} [kg]	Height [cm]	$MPA+walking_{IPAQ}$ [min/d]	$Locomotion_{QUAP}$ [h/week]	$Sitting_{QUAP}$ [h/d]	Carbohydrate intake [g/d]	Energy intake [kcal/d]	Resting heart rate [bpm]	HGS_{max} [kg]	Sex (male=0, female=1)
Variable sets																									
Full variable set	✓	✓			✓	✓	✓	✓		✓			✓	✓			✓	✓	✓	✓		✓		
No ADP	✓		✓	✓	✓	✓	✓	✓		✓			✓		✓	✓	✓	✓	✓	✓		✓		
No ADP & BIA	✓			✓	✓	✓	✓	✓		✓	✓	✓	✓			✓	✓	✓	✓	✓		✓	✓	
No QUAP	✓	✓			✓			✓	✓	✓			✓	✓			✓			✓		✓		
No IPAQ	✓	✓				✓	✓	✓					✓	✓				✓	✓	✓				
No IPAQ & QUAP	✓	✓						✓					✓	✓						✓				
No IPAQ & QUAP & ADP	✓		✓					✓		✓			✓		✓					✓		✓		
No IPAQ & QUAP & ADP & BIA	✓			✓				✓		✓	✓	✓	✓			✓				✓		✓	✓	
No Nutrition	✓	✓			✓	✓	✓			✓			✓	✓			✓	✓	✓			✓		
No Nutrition & QUAP	✓	✓			✓					✓			✓	✓			✓					✓		
No Nutrition & IPAQ	✓	✓				✓	✓			✓			✓	✓				✓	✓					
No Nutrition & IPAQ & QUAP	✓	✓								✓			✓	✓										
No Nutrition & IPAQ & QUAP & ADP	✓		✓	✓						✓			✓		✓							✓		
No Nutrition & IPAQ & QUAP & ADP & BIA	✓			✓						✓	✓		✓			✓								
No Nutrition & QUAP & ADP	✓		✓	✓	✓					✓			✓		✓	✓	✓					✓		

Table 10-17 Relative frequency with which each variable was selected using stepwise selection regression in 2000 bootstrap samples (n_b=49) drawn from the initial ActivE study dataset (n=49) considering full and reduced variable sets to recalculate AEE prediction models

Variable selection method: ***Stepwise selection***	**VM counts [cpm]**	FFM_{ADP} [kg]	FFM_{BIA} [kg]	Height [cm]	$MPA+walking_{IPAQ}$ [min/d]	$Locomotion_{QUAP}$ [h/week]	$Sitting_{QUAP}$ [h/d]	Carbohydrate intake [g/d]	Energy intake [kcal/d]	Resting heart rate [bpm]	HGS_{max} [kg]	Sex (male=0, female=1)	**Axis 1 counts [cpm]**	FFM_{ADP} [kg]	FFM_{BIA} [kg]	Height [cm]	$MPA+walking_{IPAQ}$ [min/d]	$Locomotion_{QUAP}$ [h/week]	$Sitting_{QUAP}$ [h/d]	Carbohydrate intake [g/d]	Energy intake [kcal/d]	Resting heart rate [bpm]	HGS_{max} [kg]	Sex (male=0, female=1)
Variable sets	***Bootstrap inclusion frequency [%]***												***Bootstrap inclusion frequency [%]***											
Full variable set	**88.8**	**81.1**	9.4	4.3	53.9	17.9	29.8	32.2	8.7	8.6	1.8	6.0	**88.5**	**76.3**	14.2	4.6	**68.3**	14.8	20.9	21.2	7.2	9.8	2.0	3.2
No ADP	**87.6**		**71.2**	18.4	43.1	21.1	34.9	39.0	10.9	14.6	4.9	2.1	**87.0**		**72.9**	17.2	57.7	15.9	24.8	27.1	8.3	18.3	5.1	1.4
No ADP & BIA	**83.0**			**68.4**	55.0	21.0	33.1	30.8	16.6	14.7	12.3	8.2	**82.6**			**66.1**	**67.1**	17.1	24.8	23.7	12.3	15.6	12.4	13.4
No QUAP	**95.4**	**83.2**	9.4	4.1	**70.6**			27.8	7.3	13.1	0.8	3.4	**95.8**	**78.3**	14.6	4.4	**82.6**			17.7	4.9	14.1	0.7	1.8
No IPAQ	**90.0**	**80.9**	9.6	3.8		28.4	40.0	29.0	7.5	2.8	1.7	9.0	**86.9**	**76.6**	14.7	3.9		26.7	32.6	17.2	5.8	1.9	2.0	5.6
No IPAQ & QUAP	**99.0**	**83.7**	9.7	3.5				19.5	5.2	3.3	0.4	5.1	**98.2**	**79.3**	15.2	3.3				8.7	2.3	2.1	0.4	2.7
No IPAQ & QUAP & ADP	**99.3**		**79.1**	14.1				30.2	7.8	7.8	1.9	1.6	**98.4**		**81.7**	12.9				14.9	3.3	6.0	1.8	1.4
No IPAQ & QUAP & ADP & BIA	**99.1**			**67.6**				21.8	13.6	7.2	10.5	9.3	**97.9**			**64.9**				11.7	7.5	5.4	10.4	15.4
No Nutrition	**93.0**	**85.2**	9.0	4.4	53.1	14.2	26.2			11.0	0.9	3.9	**93.8**	**80.3**	14.0	4.6	**70.0**	11.3	17.2			11.1	0.7	2.1
No Nutrition & QUAP	**97.2**	**86.5**	9.0	4.0	**68.8**					16.1	0.4	2.9	**97.9**	**81.1**	14.1	4.3	**82.5**					15.3	0.4	1.8
No Nutrition & IPAQ	**94.2**	**85.5**	9.0	3.7		23.1	35.4			3.4	0.9	6.2	**93.6**	**80.4**	14.4	3.9		22.3	29.7			2.4	0.7	3.7
No Nutrition & IPAQ & QUAP	**99.3**	**87.0**	9.0	3.2						3.7	0.3	4.5	**98.8**	**81.7**	14.4	3.3						2.2	0.3	2.7
No Nutrition & IPAQ & QUAP & ADP	**99.6**		**81.5**	15.6						10.6	1.6	1.0	**99.2**		**83.2**	13.7						6.2	1.4	1.4
No Nutrition & IPAQ & QUAP & ADP & BIA	**99.4**			**77.4**						8.2	8.8	10.9	**99.0**			**71.0**						5.5	9.0	17.5
No Nutrition & QUAP & ADP	**96.9**		**78.4**	18.6	52.8					26.4	1.8	0.9	**97.3**		**79.7**	17.1	**70.7**					30.1	1.5	1.5

Bootstrap samples were drawn with replacement. Variables were selected using stepwise selection in linear regression with p-value limits of 0.05 for the corresponding partial F-statistic for including and retaining variables in the model. Inclusion frequencies >60 % (bold printed values) indicate relevant variables.

Table 10-18 Relative frequency with which each variable was selected using LASSO in 2000 bootstrap samples (n_b=49) drawn from the initial ActivE study dataset (n=49) considering full and reduced variable sets to recalculate AEE prediction models

Variable selection method: ***LASSO (with SBC)***	**VM counts [cpm]**	FFM_{ADP} [kg]	FFM_{BIA} [kg]	Height [cm]	$MPA+walking_{IPAQ}$ [min/d]	$Locomotion_{QUAP}$ [h/week]	$Sitting_{QUAP}$ [h/d]	Carbohydrate intake [g/d]	Energy intake [kcal/d]	Resting heart rate [bpm]	HGS_{max} [kg]	Sex (male=0, female=1)	**Axis 1 counts [cpm]**	FFM_{ADP} [kg]	FFM_{BIA} [kg]	Height [cm]	$MPA+walking_{IPAQ}$ [min/d]	$Locomotion_{QUAP}$ [h/week]	$Sitting_{QUAP}$ [h/d]	Carbohydrate intake [g/d]	Energy intake [kcal/d]	Resting heart rate [bpm]	HGS_{max} [kg]	Sex (male=0, female=1)
Variable sets	***Bootstrap inclusion frequency [%]***												***Bootstrap inclusion frequency [%]***											
Full variable set	**99.1**	**86.9**	19.6	37.4	**86.2**	**77.3**	**90.5**	**80.7**	40.6	50.1	21.1	13.9	**98.9**	**87.0**	18.9	35.7	**87.6**	**68.5**	**86.9**	**77.6**	34.5	51.1	21.4	11.3
No ADP	**99.2**		**96.0**	**62.9**	**86.4**	**80.5**	**92.5**	**84.7**	42.0	**66.1**	34.7	13.8	**99.3**		**95.5**	**61.1**	**88.0**	**71.5**	**89.2**	**82.9**	36.5	**67.0**	35.7	12.0
No ADP & BIA	**99.0**			**94.6**	**86.3**	**80.3**	**91.4**	**80.5**	46.1	58.9	55.9	26.1	**99.1**			**94.8**	**87.2**	**73.8**	**88.6**	**78.2**	41.4	59.8	56.1	30.1
No QUAP	**99.8**	**87.0**	18.7	35.7	**94.9**			**74.6**	45.8	**72.2**	14.8	8.6	**99.9**	**84.1**	21.8	37.4	**96.3**			**73.5**	35.7	**70.6**	17.2	7.0
No IPAQ	**99.3**	**82.1**	27.1	27.1		**84.5**	**93.8**	**81.8**	33.3	31.0	19.7	15.2	**98.5**	**83.7**	25.0	22.9		**79.2**	**90.2**	**76.5**	28.3	26.9	19.7	12.4
No IPAQ & QUAP	**100.0**	**82.4**	21.8	18.0				**67.1**	37.5	44.7	8.4	8.9	**99.8**	**81.2**	22.5	16.1				**61.1**	28.3	39.6	8.4	6.5
No IPAQ & QUAP & ADP	**99.9**		**97.7**	39.7				**72.4**	40.3	**64.2**	21.4	9.8	**99.8**		**97.4**	36.1				**69.0**	29.8	59.4	22.6	9.0
No IPAQ & QUAP & ADP & BIA	**99.8**			**90.5**				**61.2**	44.3	51.1	47.4	21.0	**99.4**			**90.0**				58.7	34.6	47.0	47.9	26.3
No Nutrition	**99.6**	**94.1**	10.2	37.5	**84.2**	**64.9**	**88.5**			59.5	11.8	8.3	**99.7**	**92.8**	12.1	36.4	**88.5**	55.0	**86.7**			**60.2**	13.7	5.9
No Nutrition & QUAP	**99.9**	**93.5**	11.6	38.9	**95.5**					**77.4**	10.1	5.4	**100.0**	**91.4**	14.5	39.1	**97.2**					**74.5**	12.9	4.3
No Nutrition & IPAQ	**99.7**	**92.5**	13.7	27.1		**77.0**	**91.4**			42.3	11.3	10.5	**99.6**	**91.7**	13.5	22.7		**70.4**	**88.8**			35.5	12.1	7.0
No Nutrition & IPAQ & QUAP	**100.0**	**89.8**	14.4	18.9						52.5	6.8	7.6	**100.0**	**86.9**	16.8	16.9						46.0	7.7	4.6
No Nutrition & IPAQ & QUAP & ADP	**100.0**		**98.0**	48.1						**73.1**	20.2	9.1	**99.9**		**98.1**	43.2						**66.3**	21.7	8.9
No Nutrition & IPAQ & QUAP & ADP & BIA	**100.0**			**95.9**						57.3	45.6	28.0	**99.8**			**94.9**						52.3	46.6	32.3
No Nutrition & QUAP & ADP	**100.0**		**97.0**	**70.8**	**96.1**					**87.2**	27.7	8.2	**100.0**		**97.4**	**69.0**	**97.5**					**86.1**	30.3	12.5

Bootstrap samples were drawn with replacement. Variables were selected using LASSO with optimized Schwarz Bayesian Criterion (SBC). Inclusion frequencies >60 % (bold printed values) indicate relevant variables.

Table 10-19 Association of accelerometer-derived activity parameters with cardiometabolic factors using Partial Spearman rank correlation, adjusted for sex and age (n=50)

	Time in low PA [min/d]	Time in moderate PA [min/d]	Time in vigorous PA [min/d]	Time in total activity [min/d]	Proportion in low PA [%]	Proportion in moderate PA [%]	Proportion in vigorous PA [%]
	Spearman's Partial Correlation Coefficient (adjusted for sex & age) ***p-value***						
Time in low PA [min/d]	1.000						
Time in moderate PA [min/d]	0.604 ***<0.001***	1.000					
Time in vigorous PA [min/d]	0.369 ***0.010***	0.455 ***0.001***	1.000				
Time in total activity [min/d]	0.880 ***<0.001***	0.854 ***<0.001***	0.609 ***<0.001***	1.000			
Proportion in low PA [%]	0.350 ***0.015***	-0.446 ***0.001***	-0.413 ***0.004***	-0.088 *0.553*	1.000		
Proportion in moderate PA [%]	-0.330 ***0.022***	0.473 ***<0.001***	-0.119 *0.421*	-0.005 *0.973*	-0.756 ***<0.001***	1.000	
Proportion in vigorous PA [%]	0.038 *0.798*	0.127 *0.389*	0.912 ***<0.001***	0.266 *0.067*	-0.427 ***0.002***	-0.187 *0.203*	1.000
Cholesterol [mmol/l]	0.169 *0.251*	0.007 *0.965*	0.126 *0.395*	0.064 *0.664*	0.039 *0.794*	-0.131 *0.375*	0.127 *0.390*
HDL-C [mmol/l]	0.202 *0.168*	0.253 *0.082*	0.334 ***0.020***	0.253 *0.083*	-0.137 *0.352*	0.049 *0.741*	0.291 ***0.045***
LDL-C[a] [mmol/l]	0.081 *0.584*	-0.074 *0.618*	0.063 *0.668*	-0.027 *0.856*	0.048 *0.747*	-0.140 *0.344*	0.090 *0.545*
Triglycerides [mmol/l]	-0.048 *0.746*	-0.161 *0.274*	-0.182 *0.215*	-0.155 *0.294*	0.091 *0.538*	-0.013 *0.933*	-0.132 *0.371*
Cholesterol-HDL-ratio	-0.089 *0.547*	-0.254 *0.081*	-0.213 *0.146*	-0.213 *0.146*	0.162 *0.271*	-0.133 *0.369*	-0.165 *0.262*
CRP [mg/l]	-0.027 *0.853*	-0.066 *0.656*	-0.363 ***0.011***	-0.091 *0.536*	0.154 *0.295*	0.089 *0.546*	-0.376 ***0.009***
Glucose [mmol/l]	-0.271 *0.062*	-0.358 ***0.012***	-0.284 *0.050*	-0.366 ***0.010***	0.076 *0.608*	-0.052 *0.726*	-0.144 *0.328*
Insulin [mU/l]	-0.218 *0.136*	-0.143 *0.332*	-0.312 ***0.031***	-0.236 *0.107*	0.001 *0.995*	0.125 *0.398*	-0.259 *0.075*
HbA_{1c} [%]	-0.021 *0.886*	0.019 *0.896*	-0.053 *0.723*	-0.020 *0.895*	-0.128 *0.387*	0.109 *0.462*	-0.049 *0.743*
C-Peptide [ng/ml]	-0.244 *0.095*	-0.108 *0.464*	-0.182 *0.215*	-0.221 *0.131*	-0.152 *0.302*	0.169 *0.252*	-0.125 *0.398*
HOMA index	-0.242 *0.098*	-0.192 *0.192*	-0.347 ***0.016***	-0.280 *0.054*	0.024 *0.872*	0.101 *0.495*	-0.276 *0.058*

[a] LDL concentration was directly measured except for two participants; for them LDL concentration was based on calculated values. PA physical activity

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Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, dass ich die im Fachbereich Management im Gesundheitswesen der Technischen Universität Berlin eingereichte Dissertation mit dem Titel *"Development of prediction models to estimate activity-related energy expenditure under free-living conditions using accelerometry and its association with cardiometabolic factors"* selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel und Quellen verwendet habe. Die geltende Promotionsordnung der Technischen Universität Berlin (Promotionsordnung Dr. P.H. vom 16.03.1999) habe ich zur Kenntnis genommen.

Ich habe mich noch keinem anderen Promotionsverfahren unterzogen und die Dissertation nicht in der gleichen oder einer veränderten Fassung an einer anderen Fakultät oder vor einem Prüfungsausschuss einer anderen Hochschule zur Begutachtung vorgelegt.

Teile der Dissertation sind im Rahmen des Promotionsvorhabens bereits veröffentlicht worden und als solche gekennzeichnet.*

Berlin, den …… …….

Stephanie Jeran
(Dipl.-Ernährungswiss., MSc)

*** Relevante Publikationen:**

S Jeran, A Steinbrecher, T Pischon: *Prediction of activity-related energy expenditure using accelerometer-derived physical activity under free-living conditions: a systematic review* (veröffentlicht im International Journal of Obesity 2016; 40: 1187-1197)

Präsentationen

S Jeran, A Steinbrecher, T Pischon: *Prädiktion des aktivitätsabhängigen Energieumsatzes mittels akzelerometrisch erfasster körperlicher Aktivität unter Alltagsbedingungen—eine systematische Übersichtsarbeit*; Jahrestagung der Deutschen Gesellschaft für Epidemiologie (DGEpi), September 2015, Potsdam, (Postervortrag)

S Jeran, A Steinbrecher, T Pischon: *Assoziation von Dauer und Intensität körperlicher Aktivität mit metabolischen Faktoren*; Gemeinsame Jahrestagung der European Epidemiological Federation of the International Epidemiological Association (IEA-EEF), der Deutschen Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie (GMDS), und der Deutschen Gesellschaft für Epidemiologie (DGEpi), August 2016, München, (Postervortrag)

S Jeran, A Steinbrecher, J Steiniger, M Boschmann, B Brühmann, K Steindorf, T Pischon: *Prediction of activity-related energy expenditure using accelerometry-derived physical activity data under free-living conditions*; Jahrestagung der Deutschen Gesellschaft für Epidemiologie (DGEpi), September 2018, Bremen, (Postervortrag)