MISSION-T2D

Multiscale Immune System SImulator for the Onset of Type 2 Diabetes integrating genetic, metabolic and nutritional data

Work Package 5

Deliverable 5.1

Report on the specification of physical activity model input variables

European Commission

SEVENTH FRAMEWORK PROGRAMME

Document Information

Grant Agreement	**Nº**	600803	**Acronym**	MISSION-T2D
Full Title	Multiscale Immune System SImulator for the Onset of Type 2 Diabetes integrating genetic, metabolic and nutritional data			
Project URL	http://www.mission-t2d.eu			
EU Project Officer	**Name**	Dr. Adina Ratoi		

Deliverable	**No**	5.1	**Title**	Report on the specification of physical activity model input variables
Work package	**No**	5	**Title**	Modelling the effects of physical activity in T2D

Date of delivery	**Contractual**		**01 Sep 2013**			**Actual**		**23 Sep 2013**		
Status	**Version 1.3**					**Final**		**1.3**		
Nature	**Prototype**		**Report**	**X**	**Dissemination**			**Other**		

Dissemination level	Consortium+EU	X
	Public	

Target Group (If Public)		Society (in general)	
Specialized research communities		Health care enterprises	
Health care professionals		Citizens and Public Authorities	

Responsible Author	**Name**	Claudia Mazzà	**Partner**	University of Sheffield (UK)
	Email	c.mazza@sheffield.ac.uk		

Version Log

Issue Date	Version	Author (Name)	Partner
01 Sep 2013	1.1	Claudia Mazzà, Micaela Morettini, Fabio Storm, Massimo Sacchetti, Aurelio Cappozzo	USFD-UniRM
13 Sep 2013	1.2	Claudia Mazzà, Micaela Morettini, Fabio Storm, Massimo Sacchetti, Aurelio Cappozzo	USFD-UniRM

23 Sep 2013	1.3	Claudia Mazzà, Micaela Morettini. Fabio Storm, Massimo Sacchetti, Aurelio Cappozzo	USFD-UniRM

Executive Summary	This document entails the results of Task 5.1. A systematic review of the literature has been performed in order to identify the tools that are used to measure and monitor physical activity in patients with Type 2 Diabetes, with particular focus on daily life situations. An overview of the relationships found in the literature, linking physical activity measurements and type 2 diabetes related outcomes has been reported. On the basis of the results of monitoring procedure, possible inputs of physical activity model have been defined.
Keywords	Physical activity, activity monitors, chronic effects

Contents

1. Deliverable Description 5
2. Deliverable Results 5
2.1. Assessment of Physical Activity 6
2.2. Effects of Physical Activity in T2D Related Variables.....12
2.3 Ambulatory Activity and T2D Outcomes.....16
2.4 Energy Expenditure and T2D Outcomes.....18
3. Deliverable Results – Images, Tables & Graphics 18
3.1. Deliverable Images.....18
3.2. Deliverable Tables.....20
3.3. Deliverable Graphics 22

4. Deliverable Conclusions 23
4.1. Next Steps 24
5. References 25

1. Deliverable Description

This document states the results of the Task 5.1: Definition of the model input variables. A systematic review of the literature has been performed in order to identify the tools that are used to measure and monitor physical activity in patients with Type 2 Diabetes (T2D), with particular focus on daily life situations.

The objective of this systematic review is to research and evaluate the existing correlations between physical activity and T2D related variables, with special attention to inflammatory markers. In this context, attention will be focused also on discriminating between acute and chronic effects of physical activity in T2D.

2. Deliverable Results

The health benefits of a physically active lifestyle are well recognised and physical inactivity and obesity are increasingly recognised as modifiable behavioural risk factors for a wide range of chronic diseases, and in particular for Type 2 Diabetes (T2D) (Bassuk SS et al. 2005).

When referring to physically active lifestyle, the terms "physical activity", "exercise", and "physical fitness" are often confused with one another, and sometimes used interchangeably. Conversely, it is important to point out the differences between these expressions to highlight the potential differences in outcomes.

According to the classic definition given by Caspersen, "**physical activity**" is any body movement that increases energy expenditure. "**Exercise**" is a planned, structured and repetitive physical activity, while "**physical fitness**" is the capacity to perform physical activity, and makes reference to a full range of physiological and psychological qualities. Physical fitness has been also defined as 'a set of attributes that people have or achieve that relates to the ability to perform physical activity' (Caspersen CJ et al. 1985).

In this context, the terms "**non-exercise physical activity**" indicate simple non-structured activities like walking or moderate running. When referring to walking, the term "**ambulatory activity**" is also commonly used referring to the number of steps taken by an individual throughout a typical day.

Observational and clinical trial data suggest that moderate intensity physical activity such as brisk walking reduces risk of type 2 diabetes (Helmrich SP et al. 1991; Hu FB et al. 1999; Hu FB et al. 2001; Kosaka K et al. 2005; Ramachandran A et al. 2006), and all studies support the current recommendation of 2.5 h/week of a moderate aerobic activity or typically 30 min/day for 5 days/week for prevention. A meta-analysis of 10 cohort studies (Jeon CY et al. 2007) that assessed the preventive effects of moderate-intensity physical activity found that risk reduction for type 2 diabetes was 0.70 (0.58–0.84) for walking on a regular basis (typically brisk for ≥2.5 h/week).

However, balancing energy intake and expenditure is the current paradigm in promoting lifestyle-related health behaviour and is the basis for many physical activity guidelines (Haskell WL et al. 2007). From a thermodynamic point of view this focus is understandable and it is usually assumed that the beneficial effects of physical activity increase in parallel to its volume, 'the more the better'. Moreover, evidence is growing that sedentary time is a health risk factor on its own, independent of the practice of physical activity (Solomon TPJ et al. 2013).

Furthermore, 3000–4000 steps taken in a 30-minute bout are considered indicative of moderate-to-vigorous physical activity. Ideally, this would be accomplished by engaging in physical activity over and above one's usual activities of daily living.

RESULT 1: FOR THE PURPOSES OF MISSION-T2D, THE FOCUS WILL BE ON PHYSICAL ACTIVITY, AND THE INPUT TO THE MODEL THAT WILL BE DEFINED IN WP5 WILL BE ITS QUANTIFICATION IN TERMS OF NON-EXERCISE PHYSICAL ACTIVITY AND AMBULATORY ACTIVITY. THE CONCEPT OF NON-EXERCISE PHYSICAL ACTIVITY INCLUDES NON STRUCTURED ACITIVITIES LIKE WALKING AND MODERATE RUNNING.

2.1. Assessment of Physical Activity

Insight into the interaction between daily physical activity and health (i.e., the absence of physical inactivity dependent diseases) requires an objective and reliable method for the assessment of physical activity in free-living subjects. The method should be suitable to measure physical activity over periods long enough to be representative for normal daily life, with minimal discomfort to the subjects, and applicable to large populations.

As recently reviewed (Westerterp KR 2009), there are a large number of techniques for the assessment of physical activity, which can be grouped into five general categories:

- behavioural observation;
- questionnaires (including diaries, recall questionnaires and interviews);
- physiological markers like heart rate;
- indirect calorimetry (doubly labelled water or metabolic cart);
- activity monitors.

Validated techniques of estimating habitual physical activity are needed to study the relationship between physical activity and health. The greatest obstacle to validating field methods of assessing physical activity in humans has been the lack of an adequate criterion to which techniques may be compared. The interrelation of various field methods may be of some value, but because there are errors in all methods it is impossible to determine the true validity of any one of them in doing so (Montoye HJ et al. 1996).

However, indirect calorimetry, specifically the doubly labelled water method, has become the gold standard for the validation of field methods of assessing physical activity (Melanson EL et al. 1996). Doubly labelled water is a method to measure total energy expenditure (TEE) in unrestrained conditions, i.e., in individuals living in their normal surroundings over a time period of 1–4 weeks (Speakman JR 1997). However, this method does not allow quantification of the duration, frequency and intensity of physical activity performed. Metabolic cart systems which measure expired O_2 and CO_2 cannot be used over extended periods of time.

Activity questionnaires, including interviews and diaries, are the most common tools for the assessment of physical activity. The methodology is cheap and allows application in large populations. Despite the large-scale application, reliability and validity of the measurement of habitual physical activity by questionnaires is low (Shephard RJ 2003). Comparisons with doubly labelled water show generally low correlations with systematic underestimates (Staten LK et al. 2001; Arvidsson D et al. 2005; Maddison R et al. 2007; Rush EC et al. 2008), overestimates (Koebnick C et al. 2005; Mahabir S et al. 2006), or agreement at the group level with considerable error on an individual level (Bonnefoy M et al. 2001; Conway JM et al. 2002; Washburn RA et al. 2003). If the problem is that of having an instrument for simple activity-ranking, then questionnaires can be adequate and even short questionnaires can lead to surprisingly good results (Wareham NJ et al. 2003; Johansson G et al. 2008).

Heart rate monitoring is one of the first objective methods that have been proposed for the assessment of physical activity. Validation studies generally included

2–4 days continuous heart rate monitoring during the 7–14 day observation intervals with doubly labelled water. Observation days were weekdays as well as weekend days and results are weighted in a ratio according to the doubly labelled water interval. Studies apply individually assessed heart-rate energy-expenditure calibration equations for the estimation of daily energy expenditure, where equations comprise two linear regression lines, one for heart rates below and one for heart rates above the average value for sedentary activities; the so-called flex heart rate. The results of 11 different studies were reviewed in 1999 and 2005 (Westerterp KR 1999; Torun B 2005). The total energy expenditure assessed with heart rate monitoring was not different from total energy expenditure assessed with doubly labelled water at group level in all studies. However, individual differences were large as shown by the SD of the mean. The reported extremes ranged between -17% (Livingstone MB et al. 1992) and 52% (Livingstone MB et al. 1990). The heart rate monitoring is an objective method. However, the heart rate is affected by several factors besides physical activity; data conversion needs individual measurements of heart rate in combination with oxygen consumption. Nowadays, **the heart rate is applied especially as an indicator of activity intensity** (Rennie KL et al. 2005). A new application is the measurement of the heart rate in combination with body movement as a measure of physical fitness (Plasqui G et al. 2005, 2006). Those with a higher level of physical fitness can generate more activity at a lower heart rate than unfit subjects. **Additionally, the combination of heart rate measurements with accelerometry as described below, may improve precision of physical activity measurement**. However, the general shortcoming of heart rate monitoring over longer time under free-living conditions still is the data quality (Brage S et al. 2006) due to susceptibility to movement artefacts .

Activity monitors are the most promising tools for the assessment of physical activity. These sensors can be applied in free-living subjects over prolonged periods of time. When equipped with a data memory to store information on body movement, they can also be used to study patterns of physical activity in time. They can also provide an estimate of TEE and/or AEE. Total energy expenditure (TEE) is composed of activity energy expenditure (AEE), resting energy expenditure (REE; accounting for ~70% of the total) and thermogenic effect of food (accounting for ~10%).

The method of choice for the assessment of physical activity is a function of several parameters. The five methods described above were ranked on six parameters including subject interference, subject effort, providing information on activity context, providing information on activity structure, the objectivity of the data, and the time and cost involved in the application (Table 1). The ranking is a summary of the comparative

description of the separate methods where 1 denotes the highest and 5 the lowest rank.

RESULT 2: THE ACTIVITY MONITORS IN COMBINATION WITH HEART RATE MONITOR ARE THE MOST SUITABLE TOOL FOR QUANTIFYING NON-EXERCISE PHYSICAL ACTIVITY. THEY CAN BE USED AS INDICATOR OF DURATION AND INTENSITY OF NON-EXERCISE PHYSICAL ACTIVITY, RESPECTIVELY. THE MODEL TO BE DEVISED IN WP5 MUST CONSIDER RELEVANT MEASURED QUANTITIES AS INPUT.

2.1.1. Activity Monitoring

Activity monitoring refers to the use of instruments to objectively measure and record activity, posture, and motion continuously in the natural environment.

This type of devices can be divided into three categories depending on their output:

- pedometers;
- accelerometers;
- integrated multisensory systems.

Pedometers are devices that estimate the number of steps taken through mechanical or digital measurements in only the vertical plane. Accelerometers detect acceleration in one, two or three directions (uni-, bi- or triaxial accelerometers). These devices allow determination of the quantity and intensity of movements. Integrated multisensory systems combine accelerometers with other sensors that capture body response to physical activity (e.g., hearth rate or skin temperature).

Devices may differ greatly both between and within these device categories, in, for example, the types of sensors (mechanical, accelerometers, gyroscopes), number of sensors, sensor location (arm, leg, waist, multilocation), number of measurement axes (one-, two-, or three-dimensional), direction of sensitive axes, data storage (sensor and storage in 1 unit, 1 or more sensors connected to data logger), data transmission (connected to PC, internet, mobile phones), data processing and analysis (real-time, post-measurement; and fuzzy logic, neural networks, “learning” systems), outcome measures, and in the possibility of including additional signals such as heart rate, electromyogram, and electrodermal activity.

2.1.2. Validity of Activity Monitors in Chronic Diseases

With the advancement of technology, the number of activity monitors available to measure physical activity is growing. However, despite these advances, the assessment of physical activity in populations with chronic diseases (e.g., T2D) is still challenging. In fact, these patients are typically slowly moving and also small changes in physical activity are likely to be important effects of interventions.

Thus, selecting the type of activity monitor is important. Pedometers appear limited in the ability to detect certain physical activity patterns that might occur in chronic disease populations (for example, an unstable gait profile or lack of intensity of physical activity). Accelerometers can overcome this problem. Multi-axial accelerometers have the ability to measure the accelerations in different orientations, which provides information about the total amount, intensity and duration of daily physical activity. Some multisensory devices, which combine physiological parameters with accelerometers, assess both body posture and body movement.

Another factor to take into consideration is the activity monitor outcome. A systematic review conducted by Van Remoortel et al. in 2012 identified the available activity monitors that have been validated in both health and chronic disease populations. 134 validation studies were identified. Of these, 16 studies regarded chronic disease populations and in particular, only 1 Type 2 Diabetes population. The most frequently available outcomes of validated activity monitors are:

- total or active energy expenditure (TEE or AEE, respectively);
- activity count (e.g., step);
- different levels of physical activity intensity.

TEE and AEE are estimated output, whereas steps and intensity level are measured output.

Two types of validation are considered: field validation studies (validation against doubly labelled water) or laboratory validation studies (validation using metabolic cart or metabolic chamber).

When measuring TEE in field validation studies (doubly labelled water), high correlations with the TEE estimate of the activity monitor were found in most activity monitors. These correlations are, however, to a large extent driven by patient characteristics (i.e., body weight, age, height), which are important predictors of TEE. In fact, we can identify 2 types of TEE: i) related to movement and ii) related to body composition. Consequently, the comparison of TEE estimated from activity monitors, with TEE measured with indirect calorimetry or doubly labelled water is not necessarily a proof of validation.

When measuring TEE in lab validation studies by assessment of oxygen consumption, higher correlations were reported for walking activities compared to other daily life activities. This implies that the walking component of physical activity is the one that is detected better than other activities of daily living.

Most activity monitors use prediction equations to calculate energy expenditure from the activity signals. This is helpful to validate monitors against indirect calorimetry, but, given the inherent inaccuracy of these estimates and fundamental differences between the different prediction equations (some of which are proprietary to particular device manufacturers), perhaps greater weight should be given to measured monitor outputs (steps, activity counts, …) and their relation to *activity energy expenditure* (AEE), rather than the ability of a monitor to estimate energy expenditure precisely.

Accumulating evidences suggests that physical activity is highly heterogeneous and there is no single outcome measure that captures all the relevant information about a given individual.

Future studies need to capture the different physiologically important dimensions of physical activity via generation of integrated, multidimensional physical activity 'profiles' (Thompson D et al. 2013).

At present, combination of the three most frequently available outcomes of activity monitors (TEE/AEE, steps and different levels of physical activity intensity), which is like to provide a comprehensive insight in overall physical activity of a patient, is available in:

- 3 uniaxial (Actigraph, KenzLifecorder and Polar Activity Watch)
- 1 biaxial (Biotrainer Pro)
- 3 triaxial (DynaportMinimod, Actical and Actigraph GT3X)
- 2 multisensor activity monitors (SenseWear Armband and multisensor board).

In addition, another study was recently conducted (Rabinovich RA et al. 2013) for the assessment of validity of activity monitor in chronic diseases in general, and in patients with Chronic Obstructive Pulmonary Disease (COPD), in particular. This study shows that, of the 6 activity monitors considered in 14 days of continuous assessment, the DynaPortMoveMonitor and the Actigraph GT3X best explained the majority of the TEE variance not explained by body composition and showed the most significant correlations with AEE. As already mentioned, the derivation of energy expenditure is difficult by default and likely inaccurate when based on acceleration signals only, but it is important to underline that this does not render activity monitors invalid for the assessment of bodily movement and, perhaps even more importantly, intervention-associated changes.

RESULT 3: NONE OF THE COMMERCIALLY AVAILABLE ACTIVITY MONITORS HAVE BEEN SPECIFICALLY VALIDATED FOR T2D. AMONG THE OUTPUTS OF AN ACTIVITY MONITOR, THE NUMBER OF STEPS WALKED PER DAY WILL BE CONSIDERED AS THE MOST RELIABLE DAILY LIVING MEASURABLE INPUT TO THE MODEL. ENERGY EXPENDITURE AS ESTIMATED BY CURRENTLY AVAILABLE MONITORS CANNOT BE CONSIDERED AS RELIABLE.

RESULT 4: THE NUMBER OF STEPS WALKED PER DAY IN COMBINATION WITH HEART RATE WILL BE USED AS INPUTS TO WP5 MODEL.

2.2. Effects of Physical Activity in T2D Related Variables

Physical activity protective effects include both acute effects (effects of a single session) and more prolonged effects when it is repeated on a regular basis (training effect).

Regular physical activity has been shown to: improve body composition (e.g., through reduced abdominal adiposity and improved weight control); enhance lipid lipoprotein profiles (e.g. through reduced triglyceride levels, increased high-density lipoprotein (HDL), cholesterol levels and decreased low-density lipoprotein [LDL]-to-HDL ratios); improve glucose homeostasis and insulin sensitivity; reduce blood pressure; improve autonomic tone; reduce systemic inflammation; decrease blood coagulation; improve coronary blood flow; augment cardiac function; and enhance endothelial function. On the other side, acute effect may result in transient changes in the form of reductions in triglyceride levels, increases in HDL cholesterol level, decreases in blood pressure (for 12–16 hours), reductions in insulin resistance and improvements in glucose control (Bruunsgaard H, 2005).

2.2.1. Effect of Physical Activity and Exercise on Markers of Chronic-Low Grade Inflammation: Physiological Aspects

Accumulating evidences suggest that metabolic syndrome leading to Type 2 Diabetes (T2D) is determined by a state of chronic low-grade inflammation. This particular state of inflammation is not characterized by the same cytokines cascade of acute infection.

The initial cytokines that appear in the circulation in relation to an acute infection, named in order, are: TNF-α, IL-1β, IL-6 (interleukin-6), IL-1 (interleukin-1), IL-1ra (receptor antagonist), sTNF-R (soluble TNF-α-receptors) and IL-10 (Akira S et al.

1993). The systemic response known as the acute-phase response includes the production of a large number of hepatocyte-derived acute phase proteins, such as C-reactive protein (CRP) that is known to be a sensitive marker of systemic inflammation (Ross R 1999).

Chronic low-grade systemic inflammation has been introduced as a term for conditions in which a 2 to 3 fold increase in the systemic concentrations of TNF-α, IL-1, IL-6, IL-1ra, sTNF-R and CRP is reflected. In the latter case, the stimuli for the cytokines production are not known, but the likely origin of TNF-α in chronic low-grade systemic inflammation is mainly the adipose tissue (Coppack SW 2001; Hotamisligil GS 1993).

Cytokines are produced and secreted by cells and tissues not part of the immune system, (e.g., adipose tissue). The secretion of cytokines depends not only on the amount of adipose tissue but also of its location, being visceral or intra-abdominal fat more harmful than subcutaneous fat (Yudkin JS 2007).

This inflammation will lead to reduced insulin signalling, i.e., insulin resistance of tissue and organs. The resulting need will put pancreatic β-cells under chronic and increasing stress, which will induce a specific inflammation state impairing insulin production from pancreatic β-cell islets finally leading to more severe metabolic disturbances and hyperglycaemia as precursor of T2D (Dandona P et al. 2004).

In this complex framework, **physical activity and exercise offer protection against, and may be useful as a treatment for a wide variety of chronic diseases associated with chronic low-grade inflammation**.

The identification of the skeletal muscle as an endocrine organ provided a conceptual basis to understand and explain how physical activity and exercise may offer such protection.

Contracting skeletal muscles release cytokines (named myokines), which work in a hormone-like fashion, exerting their effects on other organs like liver, adipose tissue and brain. Thus, **myokines** account not only for physical activity-associated immune changes, but also **play a role in mediating the physical activity-associated metabolic changes, as well as the metabolic changes following training adaptation** (Petersen AM 2005).

To date the list of myokines includes IL-6, IL-8, and IL-15 (Pedersen BK et al. 2008). Typically, IL-6 is the first cytokine present in the circulation during exercise and the appearance of IL-6 in the circulation is by far the most marked and its appearance precedes that of the other cytokines. The level of circulating IL-6 increases in an exponential fashion (up to 100 fold) in response to exercise, and declines in the post-exercise period (Febbraio MA et al. 2002). The fact that the classical pro-inflammatory

cytokines, TNF-α and IL-1β, in general do not increase with exercise indicates that the cytokine cascade induced by exercise markedly differs from the cytokine cascade induced by infections.

The discovery that IL-6 is released from contracting skeletal muscle has generated much interest among the scientific community because this finding is somewhat paradoxical. On one hand, IL-6 is markedly produced and released in the post-exercise period when insulin action is shown to be enhanced (Wojtaszewski JF et al. 2000), but on the other hand, IL-6 has been associated with reduced insulin action and low-grade systemic inflammation (Fernandez-Real JM et al., 2003). Furthermore, the IL-6 level peak is reached at the end of the exercise or shortly thereafter (Pedersen BK et al. 2008), followed by a rapid decrease towards pre-exercise levels. **Overall, the combination of mode, intensity, and duration of the exercise determines the magnitude of the exercise-induced increase of plasma IL-6** (Febbraio MA et al. 2002)**.**

Another finding in relation to exercise is increased circulating levels of well-known anti-inflammatory cytokines, cytokine inhibitors such as IL-1ra and sTNF-R (Petersen AMW et al. 2005). Taken together, exercise provokes an increase primarily in IL-6, followed by an increase in IL-1ra and IL-10 (see Image 1). However, human skeletal muscle seems unique, in that it can produce IL-6 during contraction in the absence of any markers of inflammation and in a strict TNF-independent fashion. This finding suggests that muscular IL-6 has a role in metabolism rather than in inflammation.

Another biological role of contraction-induced IL-6 is also known to increase hepatic glucose production during exercise or lipolysis in adipose tissue. It is interesting that both intramuscular IL-6 mRNA expression and protein release are markedly enhanced when intramuscular glycogen is low, suggesting that IL-6 is somehow related to glycogen content and works as an energy sensor. In addition, many studies show that glucose ingestion during exercise attenuates the exercise-induced increase in plasma IL-6 and totally inhibits the IL-6 release from contracting skeletal muscle in humans (Pedersen BK et al. 2008).

The effect of a single bout of exercise as described above seems to be in contrast with the effect of **regular physical activity**. In fact, several epidemiological studies have reported a negative association between the amount of regular physical activity and the basal plasma IL-6 levels: **the more physically active, the lower basal plasma IL-6**.

RESULT 5: EXERCISE INDUCES AN INCREASE OF PLASMA IL-6, WHICH HAS A ROLE IN METABOLISM RATHER THAN INFLAMMATION (ACUTE EFFECT). ON THE CONTRARY, INCREASED PHYSICAL ACTIVITY FAVOURS THE LOWERING OF BASAL PLASMA IL-6. IL-6 WILL HAVE TO BE INCLUDED AMONG THE OUTPUT OF THE WP5 MODEL.

At present, evidence is limited as to whether the exercise-induced increase of plasma IL-6 is affected by training but a possible explanation could be that whereas regular exercise leads to an enhancement of glycogen synthase, and a trained muscle will consequently store more muscle glycogen, during an acute bout of exercise, the untrained muscle is highly dependent on glycogen as substrate. This means that the trained muscle uses less glycogen during work. The activation of muscle-IL-6 is glycogen dependent. At conditions with low muscle-glycogen, the transcription rate of IL-6 is faster, and relatively more IL-6 is produced at the same relative work compared with conditions with a high muscle glycogen. Thus the acute plasma IL-6 response is lower in a trained versus an untrained subject (see Image 2).

Another key point is that physical activity is known to increase insulin sensitivity (King DS et al. 1988), while, in the immediate post-exercise period, insulin action is enhanced (Wojtaszewski JF et al. 2000). In this context, the effect of IL-6 is not still elucidated. Given the different biological profiles of TNF-α and IL-6 and given that TNF-α may trigger IL-6 release, one current theory is that adipose tissue-derived TNF- α is actually the “driver” behind the metabolic syndrome and that increased systemic levels of IL-6 reflect locally produced TNF- α (Petersen AM et al. 2005). Accordingly, elevated levels of IL-6 might represent a “defence” mechanism against proinflammatory actions caused by TNF-α. An alternative hypothesis is that increased IL-6 production represents a compensatory mechanism, whereby insulin-resistant individuals or individuals at risk of developing insulin resistance stimulate an alternative mechanism with regard to maintaining glucose homeostasis. Finally, chronically elevated IL-6 levels may simply reflect a feedback mechanism due to impaired IL-6 signalling. It is, however, not known if “IL-6 resistance” exists as a phenomenon in line with the fact that a chronically elevated level of insulin most often reflects insulin resistance.

RESULT 6: INCREASED PHYSICAL ACTIVITY HAS A BENEFICIAL ROLE ON INSULIN SENSITIVITY BUT THE DEPENDENCE OF THIS FROM CITOKINES NEEDS FURTHER ELUCIDATIONS.

2.3 Ambulatory Activity and T2D Outcomes

A preliminary overview of the relationship founded in the literature between objectively measure ambulatory activity and T2D related outcomes is reported below. A more accurate analysis will be performed in Task 5.2, as foreseen in the DOW.

2.3.1 Chronic Low Grade Inflammation

As reported in 2.2.1, the exact mechanisms linking physical activity to reduced inflammation are complex and have not been fully elucidated; however, it has been suggested that the pleiotropic IL-6 may play a central role.

Very few studies have addressed the issue of short-term ambulatory activity changes on inflammatory markers. A recent study found that circulating IL-6 levels are unaltered following an acute bout of low- to moderate-intensity walking activity (Markovitch D et al. 2008). Lund et al. shows that 1 week enhancement in walking levels does not influence values for commonly used markers of chronic inflammation (IL-6 but also CRP) (Lund AJS et al. 2011). In Krogh-Madsen et al. a 2-week of substantial reduction of daily stepping does not affect IL-6 levels (Krogh-Madsen R et al. 2010). Even if further elucidation is needed, **these results suggest that the effect of acute bouts of walking activity, even if they cannot be seen in acute, can become significant at long term**.

Intervention studies, using walking as physical activity modality, have produced conflicting results, with some but not all resulting in significant reduction in markers of chronic low grade inflammation (Rokling-Andersen MH et al. 2007; Dekker MJ et al. 2007; Giannopoulou I et al. 2005; Marcell TJ et al. 2005; Wegge JK et al. 2004). However these studies are characterized by small sample sizes; the large biological and measurements inter and intra-individual variation in markers of chronic low-grade inflammation suggest that large intervention studies are needed to detect differences in these cytokines.

A study performed by Yates et al. (Yates T et al. 2010) shows that after 12 months of intervention, change in objectively measured ambulatory activity was significantly and inversely associated with IL-6 after adjustment for potential confounders, including change in BMI, suggesting mechanistic pathways between increased ambulatory activity and reduced low-grade inflammation that are independent of adiposity. A difference in change in ambulatory activity of around 2500 steps／day (equivalent to around 25 min of moderate-intensity walking activity per day (Tudor-Locke C et al. 2004)) was needed to induce each 0.5 pg／ml difference in IL-6

(see Image 3). More modest intervention may be insufficient to result in meaningful differences in markers of chronic low-grade inflammation (Yates T et al. 2010).

2.3.2 Insulin Sensitivity

The advent of objective measures of physical activity has enabled more accurate and continuous measurement of activity patterns, thus minimizing misclassification on this exposure. Theoretically, this should lead to better estimates of the association of physical activity with outcomes of interest. However, randomised trials and cohort studies incorporating objective measures of physical activity have failed to clearly identify an effect of the level of physical activity on insulin sensitivity, even in the presence of evidently reduced body fatness. As reported by Cocate et al. (Cocate PG et al. 2013), the number of steps was negatively associated with HOMA-IR (see Table 2), a recognized insulin resistance indicator, independently of age, working position, android fat, overweight/obesity prevalence, and triglycerides/HDL-c ratio. Also previous studies suggest an association between increased physical activity and increased insulin sensitivity/decreased insulin resistance. A previous cohort study has found that an increase of 2000 steps/day by sedentary individuals, 5 years after baseline, was related to higher insulin sensitivity, compared with those who practiced a lower number of steps/day (Dwyer T et al. 2011).

2.3.3 Body Composition

Visceral obesity is central to the cluster of metabolic abnormalities constituting the metabolic syndrome, which increase the risk of developing a number of diseases including T2D. There have been five major intervention trials that have studied the impact of weight loss through lifestyle interventions (healthier diet and greater exercise) on the risk of developing T2D (Paulweber T et al. 2010). These trials all showed a striking reduction in the risk of T2D (of 42–67%) with intervention, compared with control groups, despite moderate weight reductions of 0–5.6 kg. Of these trials, the United States (US) Diabetes Prevention Program (DPP) showed that for every kilogram lost, the risk of developing T2D for subjects with impaired glucose tolerance (IGT) was reduced by 16% (Paulweber T et al. 2010).

The number of steps was a negative predictor ($p < 0.05$) for total body fat, android body fat and gynoid body fat, independent of age, working position and triglycerides/HDL-c ratio (Cocate PG et al. 2013, see Table 2).

2.4 Energy Expenditure and T2D Outcomes

2.4.1 Chronic Low Grade Inflammation

Evidence suggests a positive association between REE with serum C-reactive protein (CRP) and IL-6 but the relationship between TEE and inflammatory markers has never been examined. In Lavoie et al. (Lavoie ME et al. 2010) has been shown that CRP is positively associated with daily REE (see Image 4).

Higher PAEE is a predictor of lower concentrations of CRP; instead there was no evidence of an effect of PAEE on circulating IL-6 levels even after correction for fat mass. It might be possible that IL-6 is less sensitive to change in energy expenditure than other inflammatory markers such as CRP (Lavoie ME et al. 2010).

3. Deliverable Results – Images, Tables & Graphics

3.1. Deliverable Images

Image -1

Cytokine responses to sepsis and exercise (adapted from Petersen AMW et al. 2005)

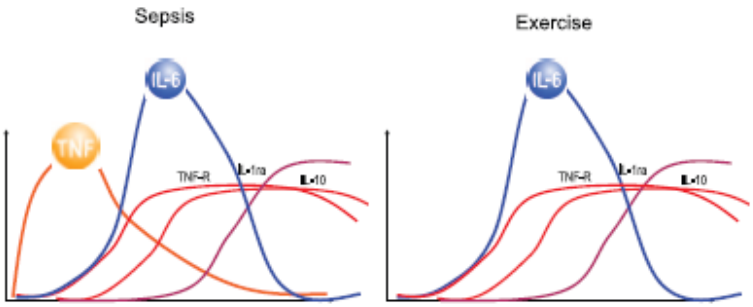


Image -2

Effect of training adaptation on IL-6 response (adapted from Pedersen BK et al. 2008)

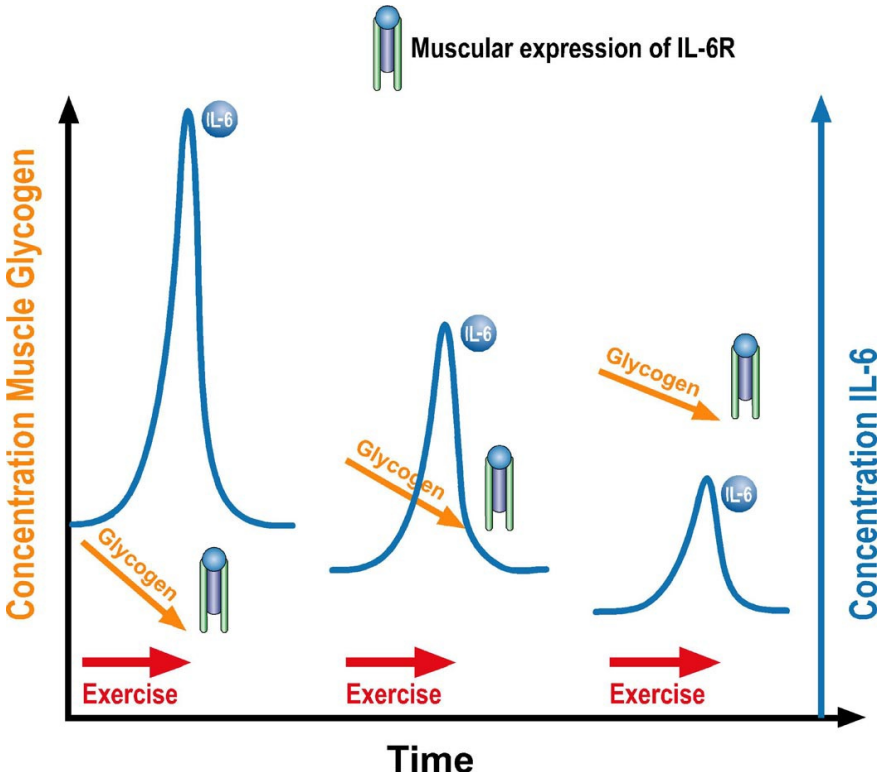


Image -3

Relationship between change in IL-6 and change in ambulatory activity (adapted from Yates T et al. 2010).

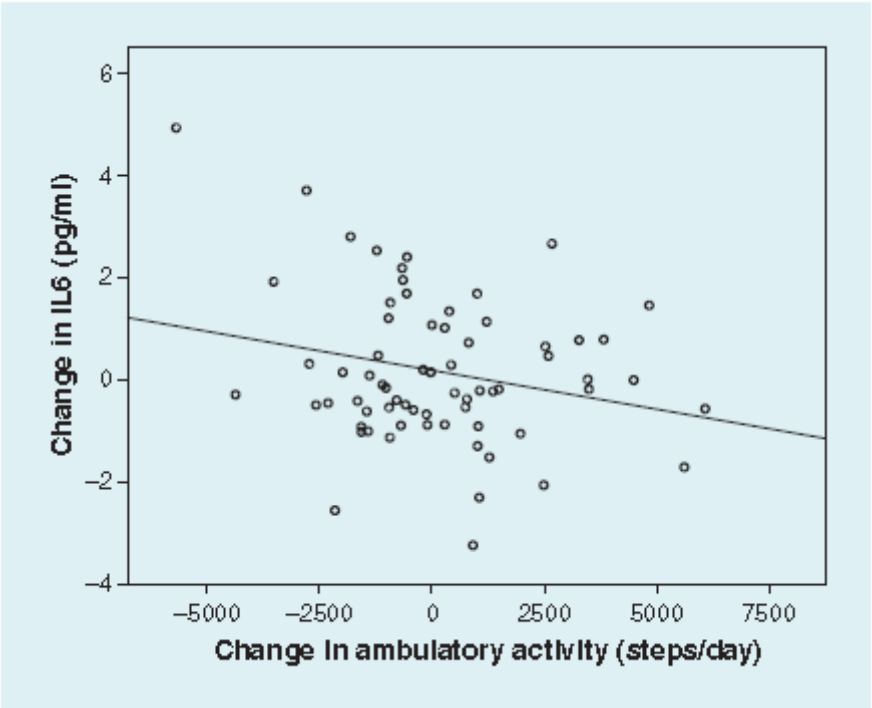
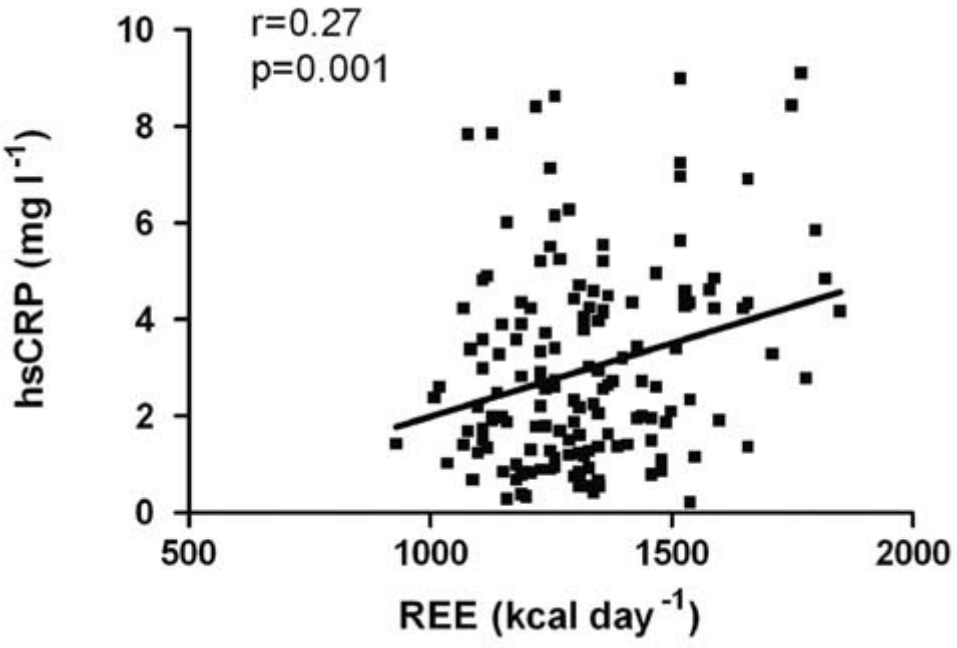


Image -4

Adapted from Lavoie ME et al. (2010)



3.2. Deliverable Tables

Table -1

Adapted from Westerterp et al. (2009)

	Subject interference	Subject effort	Contextual information	Activity structure	Objective data	Observer time/cost
Behavioural observation	5	1	1	2	4	5
Questionnaires, diaries, interviews	4	5	2	4	5	2
Hearth rate monitors	3	4	4	3	3	3
Activity monitors	2	3	3	1	2	1
Doubly labelled water	1	2	5	5	1	4

Table -2

Multiple linear regression models with the number of steps per day as the main independent variable (adapted from Cocate PG et al. 2013).

Dependent variables	β	CI 95%	R^2	p-Value
Total body fat (%)[a]	−0.000303	−0.0005; −0.0001	0.20	0.003[c]
Android fat (%)[a]	−0.000306	−0.0006; −0.0001	0.19	0.041[c]
Gynoid fat (%)[a]	−0.000340	−0.0005; −0.0001	0.18	0.001[c]
HOMA-IR[b]	−0.00002	−0.00005; −0.0000002	0.39	0.034[c]

Table -3

List of abbreviations.

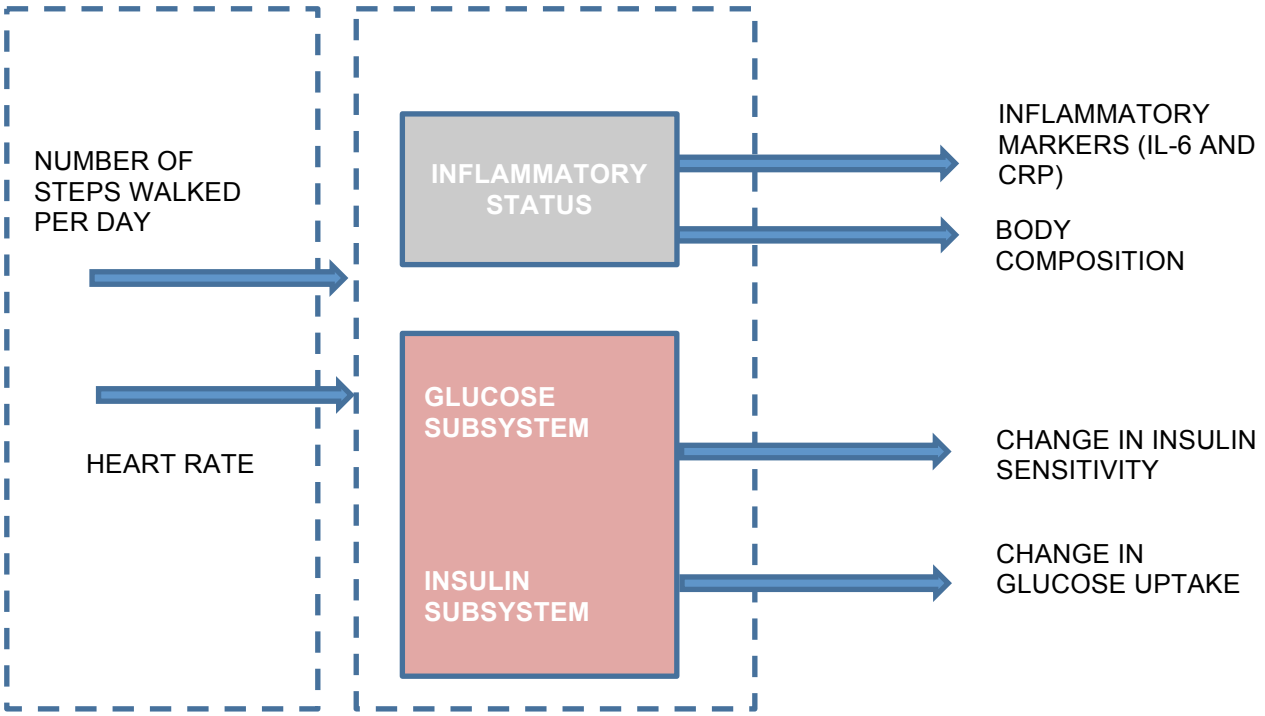
T2D	Type 2 Diabetes
TEE	Total Energy Expenditure
AEE	Active Energy Expenditure
REE	Resting Energy Expenditure
PAEE	Physical Activity Energy Expenditure
COPD	Chronic Obstructive Pulmonary Disease
LDL	Low-Density Lipoprotein
HDL	High-Density Lipoprotein
TNF-α	Tumour Necrosis Factor α
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-10	Interleukin-10
IL-15	Interleukin-15
IL-1 ra	Interleukin 1 receptor antagonist
sTNF-R	Soluble TNF-α-receptors
IL-1 β	Interleukin-1 β
CRP	C-Reactive Protein
HOMA-IR	Homeostasis Model Assessment Insulin Resistance

SD	Standard Deviation

3.3. Deliverable Graphics

Graphic -1

Structure of WP5 model.



4. Deliverable Conclusions

On the basis of the definitions of the terms “physical activity” and “exercise”, for the purposes of MISSION-T2D, the focus will be on physical activity, and in particular on non-exercise physical activity and ambulatory activity. The rationale of this is that moderate-intensity physical activity, such as brisk walking, seems to be an effective form of activity in the management and prevention of T2D. Thus, the input to the model that will be defined in WP5 will be quantification of this subcategory of physical activity in daily life.

Objective quantification of non-exercise physical activity and ambulatory activity can be made with different techniques but to date, activity monitors are the most suitable tools. Whereas validation of activity monitors in health has been already accomplished, none of the commercially available activity monitors have been specifically validated for T2D. For this reason, the number of steps walked (which is a measured output of activity monitor) but not the energy expenditure (which is an estimated output) will be considered as daily living measurable input to the model. In this context an extensive experimental study aiming at verifying validity of activity monitors on type 2 diabetic patients is desirable.

As activity monitors based on accelerometry alone are not reliable for energy expenditure determination, heart rate will be used as a supplementary input to give a more comprehensive picture of the physical activity performed in terms of duration and intensity. In fact, it was shown that heart rate correlates well with intensity of physical activity.

Effect of physical activity on T2D related outcome has been considered with the aim of giving a first overview of WP5 model outputs. The major effects can be seen on markers of systemic low-grade inflammation and in particular on IL-6 concentration, on insulin sensitivity and on adipose tissue reduction.

Exercise induces an increase of plasma IL-6, which has a role in metabolism rather than inflammation (acute effect). On the contrary, increased physical activity favours the lowering of basal plasma IL-6. IL-6 will have to be included among the output of WP5 model (see Graphic 1).

Increased physical activity has a beneficial role on insulin sensitivity but the dependence of this from cytokines needs further elucidations.

4.1. Next Steps

Next steps will be the definition and the implementation of model equations. Model equations will describe the relationships between quantification of non-exercise physical activity and T2D related variables as already mentioned.

Relationships illustrated, together with the others that will be detected in Task 5.2 will be implemented.

5. References

Akira S, Taga T, Kishimoto T (1993). Interleukin-6 in biology and medicine. Adv. Immunol. 54:1–78.

Arvidsson D, Slind F, Hulthen L (2005) Physical activity questionnaire for adolescents validated against doubly labeled water. Eur. J. Clin. Nutr. 59:376–83.

Bassuk SS, Manson JE (2005). Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. J. Appl. Physiol. 99:1193-204.

Bonnefoy M, Normand S, Pachiaudi C, Lacour JR, Laville M, Kostka T (2001). Simultaneous validation of ten physical activity questionnaires in older men: a doubly labeled water study. J. Am. Geriatr. Soc. 49:28–35.

Brage S, Brage N, Ekelund U, Luan J, Franks PW, Froberg K, Wareham NJ (2006). Effect of combined movement and heart rate monitor placement on physical activity estimates during treadmill locomotion and free-living. Eur. J. Appl. Physiol. 96:517–24.

Bruunsgaard H (2005). Physical activity and modulation of systemic low-level inflammation. J. Leukoc. Biol. 78(4):819-35.

Caspersen CJ, Powell KE, Christenson GM (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 100:126–31.

Cocate PG, de Oliveira A, Hermsdorff HH, Alfenas RD, Amorim PR, Longo GZ, Peluzio MD, Faria FR, Natali AJ (2013). Benefits and relationship of steps walked per day to cardiometabolic risk factor in Brazilian middle-aged men. J. Sci. Med. Sport Jun 3.

Conway JM, Irwin ML, Ainsworth BE (2002) Estimating energy expenditure from the Minesota Leisure Time Physical Activity and Tecumseh Occupational Activity questionnaires—doubly labeled water validation. J. Clin. Epidemiol. 55:392–9.

Coppack SW (2001). Pro-inflammatory cytokines and adipose tissue. Proc. Nutr. Soc. 60:349–56.

Dandona P, Aljada A, and Bandyopadhyay A (2004). Inflammation: the link between insulin resistance, obesity and diabetes. Trends Immunol. 25:4–7.

Dekker MJ, Lee S, Hudson R, Kilpatrick K, Graham TE, Ross R, Robinson LE (2007). An exercise intervention without weight loss decreases circulating interleukin-6 in lean and obese men with and without type 2 diabetes mellitus. Metab. Clin. Exp. 56:332–8.

Dwyer T, Ponsonby AL, Ukoumunne OC, Pezic A, Venn A, Dunstan D, Barr E, Blair S, Cochrane J, Zimmet P, Shaw J (2011). Association of change in daily step count over five years with insulin sensitivity and adiposity: population based cohort study. BMJ 342:c7249.

Febbraio MA, Pedersen BK (2002). Muscle-derived interleukin 6: mechanisms for activation and possible biological roles. FASEB J. 16:1335–47.

Fernandez-Real JM, Ricart W (2003). Insulin resistance and chronic cardiovascular inflammatory syndrome. Endocr. Rev. 24(3):278-301.

Giannopoulou I, Fernhall B, Carhart R, Weinstock RS, Baynard T, Figueroa A, Kanaley JA (2005). Effects of diet and/or exercise on the adipocytokine and inflammatory cytokine levels of postmenopausal women with type 2 diabetes. Metab. Clin. Exp. 54: 866–75.

Haskell WL, Lee I-M, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A (2007). Physical Activity and Public Health: Updated Recommendation for Adults from the American College of Sports Medicine and the American Heart Association. Med. Sci. Sports Exerc. 39:1423–34.

Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS Jr (1991). Physical activity and reduced occurrence of non–insulin-dependent diabetes mellitus. N. Engl. J. Med. 325(3):147–52.

Hotamisligil GS, Shargill NS, Spiegelman BM (1993). Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 259:87–91.

Hu FB, Sigal RJ, Rich-Edwards JW, Colditz GA, Solomon CG, Willett WC, Speizer FE, Manson JE (1999). Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. JAMA 282(15):1433–9.

Hu FB, Stampfer MJ, Solomon C, Liu S, Colditz GA, Speizer FE, Willett WC, Manson JE (2001). Physical activity and risk for cardiovascular events in diabetic women. Ann. Intern. Med.134(2):96–105.

Jeon CY, Lokken RP, Hu FB, van Dam RM (2007). Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. Diabetes Care 30(3): 744–52.

Johansson G, Westerterp KR (2008). Assessment of the physical activity level with two questions: validation with doubly labeled water. Int. J. Obes. 32:1031–3.

King DS, Dalsky GP, Clutter WE, Young DA, Staten MA, Cryer PE, Holloszy JO (1988). Effects of exercise and lack of exercise on insulin sensitivity and responsiveness. J. Appl. Physiol. 64:1942–6.

Koebnick C, Wagner K, Thielecke F, Moeseneder J, Hoehne A, Franke A, Meyer H, Garcia AL, Trippo U, Zunft HFJ (2005). Validation of a simplified physical activity record by doubly labeled water technique. Int. J. Obes. 29:302–9.

Kosaka K, Noda M, Kuzuya T (2005). Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. Diabetes Res. Clin. Pract. 67(2): 152–62.

Krogh-Madsen R, Thyfault JP, Broholm C, Mortensen OH, Olsen RH, Mounier R, Plomgaard P, van Hall G, Booth FW, Pedersen BK (2010). A 2-wk reduction of ambulatory activity attenuates peripheral insulin sensitivity. J. Appl. Physiol. 108:1034–40.

Lavoie ME, Rabasa-Lhoret R, Doucet E, Mignault D, Messier L, Bastard JP, Faraj M (2010). Association between physical activity energy expenditure and inflammatory markers in sedentary overweight and obese women. Int. J. Obes. (Lond). 34(9):1387-95.

Livingstone MB, Coward WA, Prentice AM, Davies PS, Strain JJ, McKenna PG, Mahoney CA, White JA, Stewart CM, Kerr MJ (1992). Daily energy expenditure in free-living children: comparison of heart-rate monitoring with the doubly labeled (2H2(18)O) method. Am. J. Clin. Nutr. 56:343–52.

Livingstone MB, Prentice AM, Coward WA, Ceesay SM, Strain JJ, McKenna PG, Nevin GB, Barker ME, Hickey RJ (1990). Simultaneous measurement of free-living energy expenditure by the doubly labeled water method and heart-rate monitoring. Am. J. Clin. Nutr. 52:59–65.

Lund AJS, Hurst TL, Tyrrel RM, Thompson D (2011). Markers of Chronic Inflammation with Short-Term Changes in Physical Activity. Med. Sci. Sports Exerc. 43(4): 578–83.

Maddison R, Mhurchu CN, Jiang Y, Vander Hoorn S, Rodgers A, Lawes CMM, Rush E (2007). International Physical Activity Questionnaire (IPAQ) and New Zealand Physical Activity Questionnaire (NZPAQ): a doubly labeled water validation. Int. J. Behav. Nutr. Phys. Act. 4:62.

Mahabir S, Baer DJ, Giffen C, Clevidence BA, Campbell WS, Taylor PR, Hartman TJ (2006). Comparison of energy expenditure estimates from 4 physical activity questionnaires with doubly labeled water estimates in postmenopausal women. Am. J. Clin. Nutr. 84:230–6.

Marcell TJ, McAuley KA, Traustadottir T, Reaven PD (2005). Exercise training is not associated with improved levels of C-reactive protein or adiponectin. Metab. Clin. Exp. 54: 533–41.

Markovitch D, Tyrrell RM, Thompson D (2008). Acute moderate-intensity exercise in middle-aged men has neither an anti- nor proinflammatory effect. J. Appl. Physiol. 105:260–5.

Melanson EL, Freedson PS (1996). Physical activity assessment: a review of methods. Crit. Rev. Food Sci. Nutr. 36:385–96.

Montoye HJ, Kemper HCG, Saris WHM, Washburn RA (1996) Measuring physical activity and energy expenditure. Human Kinetics, Champaign.

Paulweber B, Valensi P, Lindstrom J et al (2010). A European evidence-based guideline for the prevention of type 2 diabetes. Horm. Metab. Res. 42 (1):S3–36.

Pedersen BK, Akerstrom TC, Nielsen AR, Fischer CP (2007). Role of myokines in exercise and metabolism. J. Appl. Physiol. 103: 1093–8.

Pedersen BK, Febbraio MA (2008). Muscle as an Endocrine Organ: Focus on Muscle-Derived Interleukin-6. Physiol. Rev. 88:1379–406.

Petersen AM, Pedersen BK (2005). The anti-inflammatory effect of exercise. J. Appl. Physiol. 98: 1154-62.

Plasqui G, Westerterp KR (2005). Accelerometry and heart rate as a measure of physical fitness: proof of concept. Med. Sci. Sports Exerc. 37:872–6.

Plasqui G, Westerterp KR (2006). Accelerometry and heart rate monitoring as a measure of physical fitness: cross-validation. Med. Sci. Sports Exerc. 38:1510–4.

Rabinovich RA, Louvaris Z, Raste Y, Langer D, Remoortel HV, Giavedoni S, Burtin C, Regueiro EM, Vogiatzis I, Hopkinson NS, Polkey MI, Wilson FJ, Macnee W, Westerterp KR, Troosters T; PROactive consortium (2013). Validity of physical activity monitors during daily life in patients with COPD. Eur. Respir. J. Feb 8.

Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme (IDPP) (2006). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia. 49(2):289–97.

Rennie KL, Livingstone BE, Wells JCK, McGloin A, Coward WA, Prentice AM, Jebb SA (2005). Association of physical activity with body-composition indexes in children aged 6–8 y at varied risk of obesity. Am. J. Clin. Nutr. 82:13–20.

Rokling-Andersen MH, Reseland JE, Veierød MB (2007). Effects of longterm exercise and diet intervention on plasma adipokine concentrations. Am. J. Clin. Nutr. 86:1293–301.

Ross R (1999). Atherosclerosis — an inflammatory disease. N. Engl. J. Med. 340:115–26.

Rush EC, Valencia ME, Plank LD (2008). Validation of a 7-day physical activity diary against doubly-labelled water. Ann. Hum. Biol. 35:416–21.

Shephard RJ (2003) Limits to the measurement of habitual physical activity by questionnaires. Br. J. Sports Med. 37:197–206.

Solomon TP, Thyfault JP (2013). Type 2 diabetes sits in a chair. Diabetes Obes. Metab. Apr. 3.

Speakman JR (1997). Doubly-labelled water: theory and practice. Chapman & Hall, London

Staten LK, Taren DL, HowellWH, TobarM, Poehlman ET, Hill A, Reid PM, Ritenbaugh C (2001). Validation of the Arizona activity frequency questionnaire using doubly labeled water. Med. Sci. Sports Exerc. 33:1959–67.

Thompson D, Batterham AM (2013). Towards Integrated Physical Activity Profiling. PLoS ONE 8(2): e56427.

Torun B (2005). Energy requirements of children and adolescents. Public Health. Nutr. 8:968–93.

Tudor-Locke C, Bassett DR Jr (2004). How many steps ⁄ day are enough? Preliminary pedometer indices for public health. Sports. Med. 34: 1–8.

Van Remoortel H, Giavedoni S, Raste Y, Burtin C, Louvaris Z, Gimeno-Santos E, Langer D, Glendenning A, Hopkinson NS, Vogiatzis I, Peterson BT, Wilson F, Mann B, Rabinovich R, Puhan MA, Troosters T; PROactive consortium (2012). Validity of activity monitors in health and chronic disease: a systematic review. Int. J. Behav. Nutr. Phys. Act. 9:84.

Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S, Day NE (2003). Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health. Nutr. 6:407–13.

Washburn RA, Jacobsen DJ, Sonko BJ, Hill JO, Donnelly JE (2003). The validity of the Stanford seven-day physical activity recall in young adults. Med. Sci. Sports Exerc. 35:1374–80.

Wegge JK, Roberts CK, Ngo TH, Barnard RJ (2004). Effect of diet and exercise intervention on inflammatory and adhesion molecules in postmenopausal women on hormone replacement therapy and at risk for coronary artery disease. Metab. Clin. Exp. 53: 377–81.

Westerterp KR (1999). Assessment of physical activity level and energy expenditure of activity: current evidence and research issues. Med. Sci. Sports Exerc. 31:S522–5.

Westerp KR (2009). Assessment of physical activity: a critical appraisal. Eur. J. Appl. Physiol. 105:823–8.

Wojtaszewski JF, Hansen BF, Gade Kiens B, Markuns JF, Goodyear LJ, Richter EA (2000). Insulin signaling and insulin sensitivity after exercise in human skeletal muscle. Diabetes 49: 325–31.

Yates T, Davies MJ, Gorely T, Talbot D, Bull F, Sattar N, Khunti K (2010), The effect of increased ambulatory activity on markers of chronic low-grade inflammation: evidence from the PREPARE programme randomized controlled trial. Diabet. Med. 27:1256–63.

Yudkin JS (2007). Inflammation, obesity, and the metabolic syndrome. Horm. Metab. Res. 39:707–9.