Physical activity and chronic disease risk: development and evaluation of a physical activity index and baseline physical activity data calibration in EPIC Germany.

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List of abbreviations

AC – accelerometer counts

ALPHA – ALPHA environmental questionnaire

B.C. – Before Christ

BMI – Body Mass Index

β_0 – intercept

β – beta coefficient

CCTV – closed circuit television

CHD – coronary heart disease

CI – confidence intervals

CVD – cardiovascular diseases

DAG – directed acyclic graph

DLW - double labeled water

EE – energy expenditure

EPIC – European Prospective Investigation into Cancer and Nutrition Study

EPIC-PAQ2 – EPIC Physical Activity Questionnaire 2

FP – fractional polynomial

g – gram

GPS - Global Positioning System

HR – hazard rate

IPAI – Improved Physical Activity Index

kcal – kilocalories

kg – kilogram

MET – metabolic equivalents

MI – myocardial infarction

MVPA – moderate and vigorous physical activity

n – sample size

p – p value

PA – physical activity

PAEE – physical activity energy expenditure

PAL – physical activity level

PC – personal computer

Pct –percentile

Qb_{AC} – Questionnaire-based accelerometer counts

r – correlation coefficient

R^2 - coefficient of determination

REE – resting energy expenditure

RPAQ – Recent Physical Activity Questionnaire

RR – risk ratio

SD – standard deviation

TEE – total energy expenditure

TV – television viewing

U – observation error in an error model

W – observation related to X

WHO – World Health Organization

X – covariate measured with error/ truth

Y – response

Z – covariate measured without error

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Preface

"I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science, whatever the matter may be."

This quotation by William Thompson, accompanied my PhD journey from the first day on. Even if William Thompson was a physicist his words comprise one of the most important issues in epidemiology: finding the best possible measure for exposure and outcome in order to improve the precision in estimating risk-models for diseases.

Therefore, the overall aim of this PhD thesis was to enhance the physical activity measurement methods and tools currently used in EPIC Germany and develop better methods for future use.

1. Introduction

Physical activity (PA) is a lifestyle factor that has been shown to prevent chronic diseases (1). The accurate PA measurement is essential to estimate the true magnitude of the relationship between PA and disease risk. However, PA is not easy to assess. On the one hand, the gold standard of measuring free-living PA is double labeled water (DLW) but the high costs make it impossible to use in large epidemiological studies. On the other hand, the easiest way to assess PA is by applying questionnaires. Therefore, a researcher has to balance between validity and application convenience. In the majority of the cases, the decision is made in favor of a questionnaire.

Until today, questionnaires have been the most widely used PA measurement method even though they are highly prone to measurement error (2) despite a constant development to improve their accuracy.

In the European Prospective Investigation Into Cancer and Nutrition Study EPIC two questionnaires have found their way: the EPIC Physical Activity Questionnaire 2 (EPIC-PAQ2) that measures PA of the last 12 months (3) and The Recent Physical Activity Questionnaire (RPAQ) (4) with a time frame of one month. Both questionnaires enable the calculation of PA indices: the Cambridge Index and the Total Physical Activity Index which categorize their participants' activity into 4 categories: inactive, moderately inactive, moderately active and active. Those indices were developed for adult populations and consider PA at work as a high impact item by cross-classifying the recreational activity level with occupational activity. Furthermore, sedentary activities are not taken into account in these indices. A recent RPAQ validation study in the EPIC cohort with currently used indices, although showed fair validity. Of three indices the Cambridge Index seemed to be the most useful to rank habitual physical activity of individuals across European populations. Total Physical Activity Index and the Recreational Index showed less satisfying results (4).

Nowadays, objective measurement methods for PA have been developed and improve the challenging task of measuring the individuals' PA level. Moreover, they allow the researchers to calibrate their data, taking into account the measurement error of questionnaires and thereby, improve the estimation of the relationship magnitudes between PA and a chosen outcome.

Taking advantage of those innovations to improve the measurement accuracy is a researchers' obligation. PA data calibration enables a re-estimation of the true relationship between PA and chronic disease risk and also improves the accuracy of estimates where PA acts as a confounder. The consequential conclusions may have public health implications.

2. Aims and structure of the thesis

The following objectives were pursued:

- Development and evaluation of a valid physical activity index – the Improved Physical Activity Index (IPAI), which will be able to categorize people into activity categories but may also be used as a continuous measure that reflects one's activity amount (movement).
- Calibration of the available baseline PA questionnaire measurement in EPIC Germany. Therefore, a statistical model, estimated from the EPIC sub-sample (2010-2013) will be developed, based on the objective PA measure and the EPIC-PA questionnaire. Baseline self-reported PA will be calibrated using the best fitting statistical model based on the objective PA measurement in the sub-sample.
- Estimation of the associations between calibrated and non-calibrated baseline PA data and risk of overall chronic diseases, type 2 diabetes, myocardial infarction, stroke and cancer. The risk of chronic diseases will be estimated using Cox proportional hazards regression in the whole EPIC-Germany cohort.

These objectives were accomplished by applying an extensive physical activity questionnaire and a 7-day heart rate and acceleration sensor PA measurement to a sub-sample of older adults from EPIC-Germany.

The present thesis is structured as follows: In chapter 3, background information about PA and available measurement methods for PA assessment is given. Furthermore, statistical models for calibration will be discussed and finally a literature review about the current knowledge of the associations between PA and chronic disease risk is presented.
The methods section gives a detailed description on the populations and statistical methods used. The statistical methods section (chapter 4.5) is divided into 3 sub-sections to distinguish the methods used for each objective. Similarly structured is the results section which presents, in chapter 5, the results on the development and evaluation of the IPAI and in chapter 6 the results on the calibration and disease risk estimation. The thesis concludes with a detailed discussion in chapter 7 and overall conclusion in chapter 8.

3. Background

3.1 Physical activity

3.1.1 Definition and guidelines

In common parlance PA, fitness, sports and exercise are used interchangeably. Nevertheless, in science there are very specific differences between these terms and they have also a different effect on health. PA is defined as any bodily movement produced by skeletal muscles that requires energy expenditure (5). It is the sum of exercise and non-exercise activity. Exercise is a planned, structured and repetitive bodily movement, being a subcategory of PA that is performed to improve or maintain one or more components of physical fitness (5). From this perspective sport is a major part of exercise. The Council of Europe defines sport as "*all forms of physical activity which, through casual or organized participation, aim at expressing or improving physical fitness and mental well-being, forming social relationships or obtaining results in competition at all levels*" (6). Physical fitness is defined as a set of attributes related to the ability to perform PA that people have or achieve (5).

PA belongs to the daily life of humans since mankind exists. Hunters in the Paleolithic Era maintained a routine of 1 or 2 days of intense exertion and rested in the next 2 days. During the resting days, however, less intense 6 to 20 mile trips were undertaken (7). Ancient China as well as India (3000 to 1000 B.C.) developed principles of life in harmony with the world, with exercise being a mainstay of their concepts. Also the ancient Greeks who promoted exercise and health induced body shape and conducted the Olympic Games (8).
Connections between PA and medicine are attributed to Herodicus (ca. 480 B.C.) who was the first to prescribe gymnastics as a therapy. Hippocrates, assumed that "*(…) food and exercise, while possessing opposite qualities, yet work together to produce health*" (9) and Gallen described in detail the healthfulness of exercise in his book *On Hygiene.* Until the 18th century the ancient Greek view was still widely accepted, nevertheless, pioneering physicians added more knowledge into the state of art about the importance of maintaining an active lifestyle.
Nowadays, PA belongs to our lifestyle and is considered as one of the major factors preventing chronic diseases and helping maintain a healthy living. The latest guidelines for adults aged 18-64, from the World Health Organization (WHO) state that, in order to improve cardiorespiratory, muscular fitness, bone health and to reduce the risk of non-communicable diseases and depression the following amount of PA should be maintained (10):

- "At least 150 minutes of moderate-intensity aerobic PA throughout the week, **or** do at least 75 minutes of vigorous-intensity aerobic PA throughout the week, **or** an equivalent combination of moderate- and vigorous-intensity activity.
- Aerobic activity should be performed in bouts of at least 10 minutes duration.
- For additional health benefits, adults should increase their moderate-intensity aerobic PA to 300 minutes per week, **or** engage in 150 minutes of vigorous-intensity aerobic PA per week, **or** an equivalent combination of moderate- and vigorous-intensity activity.
- Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week."

3.1.2 Measuring physical activity

There are different methods to assess PA. Below a list of available methods for PA measurement is presented (11):

Not-individual:

- Number of cars per household
- Number of bicycles per household
- Closed circuit television (CCTV) (People density)

Subjective (individual):

- Job classification
- Questionnaires
- Activity diaries
- Proxy-reports (parents – child)
- Recalls

Objective:

- DLW
- Direct calorimetry
- Indirect calorimetry
- Accelerometer
- Heart rate monitors
- Global positioning systems (GPS) and other location systems
- Galvanic skin response
- Observation

Before choosing a method it is important to determine what really should be measured. There are different factors (dimensions) that characterize PA (12):

- **Type:** The PA type, i.e. sport, swimming, running, gardening, walking
- **Frequency:** How often in what time span (i.e. 3 times a week)
- **Duration:** The duration of the PA: hours, minutes, seconds etc.
- **Intensity:** Intensity refers to the physical effort required to perform the activity (metabolic equivalents per hour (MET/h))
- **Magnitude:** The sum of the above
- **Setting/Context:** refers to the purpose or circumstances under which activities are performed i.e. At work, fitness center, at home

3.1.3 Questionnaires

Physical activity questionnaires (PAQ) are the most widely used method to assess long term PA. Especially in large-scale studies questionnaires are the most feasible method.

There is a plethora of questionnaire types trying to capture as good as possible PA amount of an individual. Some questionnaires concentrate on the activity during the last year, some on the activity in the last week and others only on habitual activities. Different methods, including scores and categories, are used in order to determine the participants' PA level. It is differentiated between (12):

- Recall questionnaires, which contain 5 – 15 items, typically cover a time frame of a week or a month. They intend to categorize the individuals in PA categories: inactive, moderately inactive, moderately active, active, etc.
- Quantitative history questionnaires, which contain 15 – 60 items with a variable time frame, from a week to a lifetime. They intend to gather information about different PA dimensions, including PA patterns, types, duration, intensity, setting etc. and domains: occupation, household, transport, leisure. Furthermore, they may estimate physical activity energy expenditure (PAEE) via assigning MET/h estimations from the Compendium of Physical Activity to the activities of the respondent (13).
- Global self-reports, which contain 1 – 4 items, with a long time frame (years). They intend to categorize the participants in PA categories and aim to reduce bias arising from shorter time frames by pooling weekly and seasonal variability in PA.

Questionnaires may be completed on paper, via interview or on web-enabled versions. They have to be well formatted and easy to read for the participants' convenience (12).

Type of activity and the corresponding MET values are often used as a measure of intensity in order to calculate ones PA magnitude. Nevertheless, they are just a crude measure and do not reflect the individual load which differs between obese and non-obese people (14, 15).

In a systematic review of 31 new PAQs and 96 existing (previously published test results) PAQs, the median validity of existing PAQs ranged from r=0.30 to r=0.39 and for new PAQs from r=0.25 to r=0.41 (16). The reliability ranged from r=0.62 to r=0.76. Four of the reviewed PAQs showed acceptable results for validity and reliability: the International Physical Activity Questionnaire, the Flemish Physical Activity Computerized Questionnaire, the Previous Day Physical Activity Recall and the Revised Physical Activity Readiness Questionnaire (16).

A further review, concerning the validity of measuring PAEE by questionnaires, it became clear that among the PAQs that try to estimate PAEE only few show acceptable criterion validity (2). The two best PAQs indicated a mean difference in total energy expenditure (TEE) (TEE_{PAQ} – TEE_{DLW}) of 10% and 2%, and correlation coefficients of 0.62 and 0.63.

In summary, the most important advantages that make questionnaires the most widely used method are: a low cost, the possibility to define a time frame, suitability for most populations, a low respondent burden, an ease in data collection and analysis, the non-reactiveness and the possibility to precisely define the required PA dimension. On the other hand, questionnaires have also disadvantages. These include: a high possibility of recall bias that becomes bigger the longer the time frame, the social desirability and cultural dependency, the non-suitability for young children or cognitive impaired older adults, the need for adaptation and modification of the questionnaire to match the specific study population, and a high measurement error in estimating measures of PA like PAEE, MET/h or hours spent in PA/period of time.

3.1.4 Objective measures of physical activity

An alternative to measurement of PA by questionnaire is the application of objective measurement methods. Below, a short outline on the working principles, validity, reliability and cost of selected objective PA measurement methods is given.

Double labeled water

The DLW method, developed by Lifson et al. (17) in 1949 uses stable isotopes of hydrogen and oxygen and is considered to be the **gold standard** in measuring free living energy expenditure (EE).

The method is completely safe for the subject, requires periodic sampling of body fluids, is non-restrictive, and is suited for measurement of EE in free-living or hospitalized patients. Also elderly, pregnant women, children, neonates and breastfed infants can safely take part in studies with DLW and provide samples for analysis.

After the administration of DLW ($^2H_2{}^{18}O$), the labeled hydrogen ($^2H_2$) will be eliminated as water (^2H_2O), corresponding to water output, whereas the oxygen isotope will be eliminated as water ($H_2{}^{18}O$) and as expired carbon dioxide ($C^{18}O_2$). A diet record for the study period is needed in order to predict the respiratory quotient (VCO_2/VO_2) from food composition data (18). Alternatively, respiratory quotients can be measured directly by respiratory gas exchange measurements. By measuring the difference between the elimination rates of labeled oxygen and hydrogen, the VCO_2 production rate can be calculated and converted into EE by Weir's equation (19):

$$REE = [VO_2\,(3.94) + VCO_2\,(1.11)]\,1440 min/day \qquad [1.0]$$

where REE is resting energy expenditure.

A typical study protocol using the DLW method starts with a urine collection, before dose administration, to determine baseline values for the hydrogen and oxygen isotopes. The subject receives a single oral bolus dose of heavy water ($^2H_2{}^{18}O$). Generally, adults are given

a dose consisting of 0.15g $H_2{}^{18}O$/kg body weight and 0.06g ^2H_2O/kg body weight. Children and neonates are given higher doses due to their faster water turnover rates. Following the DLW administration, urine will be collected during the observation period. Two study designs have been validated to measure energy expenditure, one by Schoeller et al. (20) and another protocol reported by Klein et al. (21). The study period ends after 7 to 21 days when a urine sample is collected to close the measurement period. The optimal metabolic period for observation is predicted to be between 0.5 and 3 biological half-lives of water. The subject is free to engage in normal activities during the measurement.
The cost for a single heavy water dose for adults lies between $300 and $500. Besides the high price and the need for sophisticated equipment, it is important to remember that DLW does neither provide data on day-to-day changes in TEE, nor on the daily pattern of PA. PAEE is estimated from TEE and not measured directly. To perform the DLW analysis experienced staff and scientists are needed.

Calorimetry

Calorimetry can be named the second standard in estimating energy expenditure (EE). It is based on the principle that the oxygen and carbon dioxide that a person inhales and exhales correlates with the heat production. In other words, by assessing oxygen consumption (or heat) it measures EE (12). Calorimetry can be performed in two ways: directly and indirectly.

Direct calorimetry requires isolating the individual in special chambers for a given period of time (Figure 1). Depending on the measurement purpose it can take from several minutes (for particular PA, for example cycling) up to a few days (for a fix living schedule) (22). TEE is measured through production of heat. PAEE is estimated from the relation of REE, thermic response to meals to TEE (23). These requirements are among the reasons that make the direct calorimetry method expensive. Nevertheless, the estimation of TEE is burdened with only a 1% measurement error.

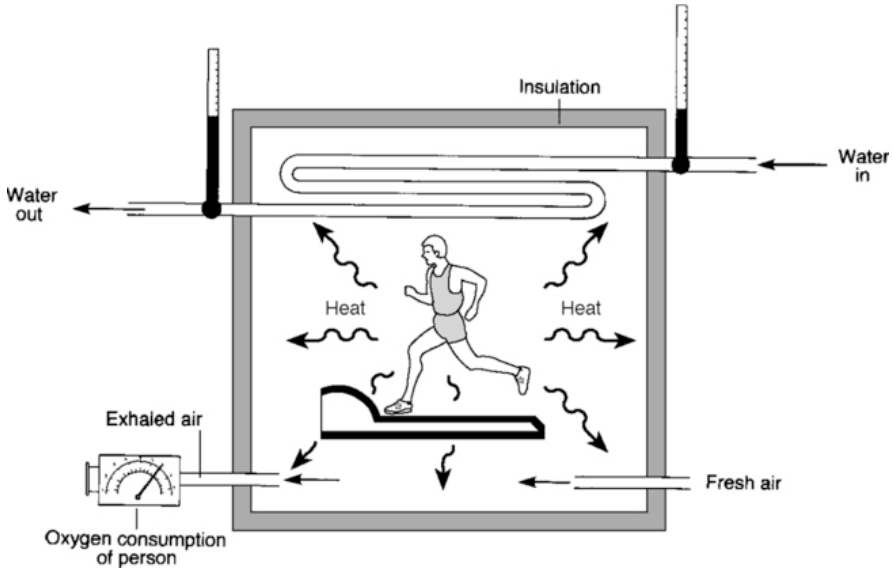


Figure 1 Direct calorimetry chamber
Source:primalmeded.com

Indirect calorimetry is less expensive. The participants breath room air through a face mask, a mouth piece with a nose clip, a canopy hood or an endotracheal tube (for mechanically ventilated patients in clinical use) (Figure 2) (24, 25). The carts are mostly big and bulky, what makes them suitable for laboratory conditions but not for free living populations. Moreover, depending on the skills of the operator and the equipment status, measurement error may occur. Portable metabolic carts have been developed and are already in use, but their measurement error is higher than that of the stationary ones. Besides, they can affect the PA of the carrier (26). The gas is collected and measured by gas sensors and transformed into values for REE (27). The VO_2 and VCO_2 can be calculated by Weir'e equation [1.0] info EE (19).

PAEE is computed by association with REE and the specific dynamic action of nutrients. Therefore, it is important to either collect a 24h recall from the participant or provide a meal to the participant (24). Also, personal details should be collected before the measurement, for a better interpretation of the data (12).

This method is not suitable for large epidemiological studies, because of its expensiveness and difficulty in implementation (12). Free living studies are rather hard to perform, because the measurement time period does not exceed 24 hours and normal PA patterns are being inhibited (23). The method is practical for validation studies of objective measures like accelerometers or heart rate monitors, but because of mentioned limitations, it should not be used to validate questionnaires. Indirect calorimetry can be successfully used in controlled experiments, where treatment effects are being investigated (example, mechanically ventilated patients). The reliability and validity is limited to specific tasks as described above and the measurement error varies from 2-3% (23).

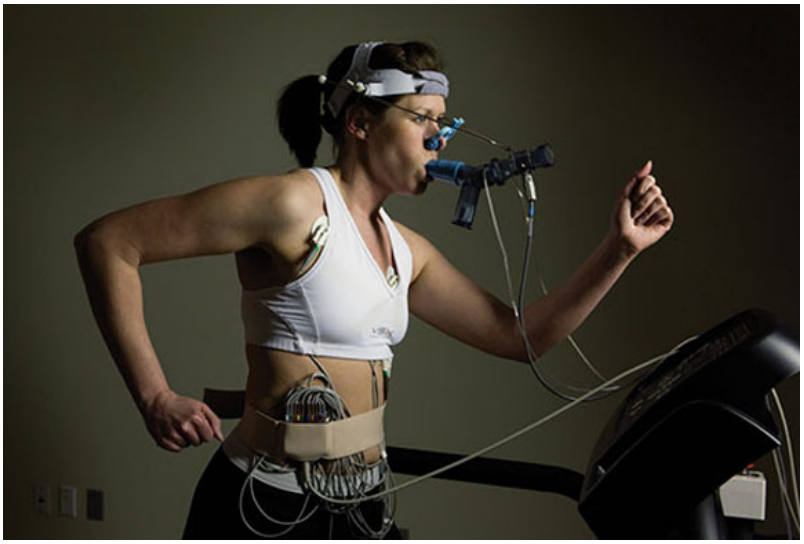


Figure 2 Indirect calorimetry measurement during treadmill test
Source: carefusion.com

Accelerometers

Accelerometers are a recent development in objective PA measurement. They are small, light and discrete. Usually the device is attached by a strap to the hip or wrist but other placements like the lower back, ankle or tight are also possible.

Accelerometers operate by measuring acceleration along an axis (uniaxial) or more than one axis (biaxial or triaxial accelerometers) using different technologies including piezoelectric, micromechanical springs, and changes in capacitance (28). The sensor converts acceleration into electrical signals that are proportional to the mechanical force producing acceleration (Figure 3). Electrical signals are then converted trough an analog-digital converter, eventually filtered and then usually integrated over a defined time period. While the dynamic range is defined by the sensor, in newer accelerometers the sampling frequency and the time resolution are modifiable by the researcher. The output is called count and has no dimension. In a second step these counts can be converted into estimations of EE by different formulas (29). Several analytic techniques are available to convert the activity measurements in valid estimates of EE.

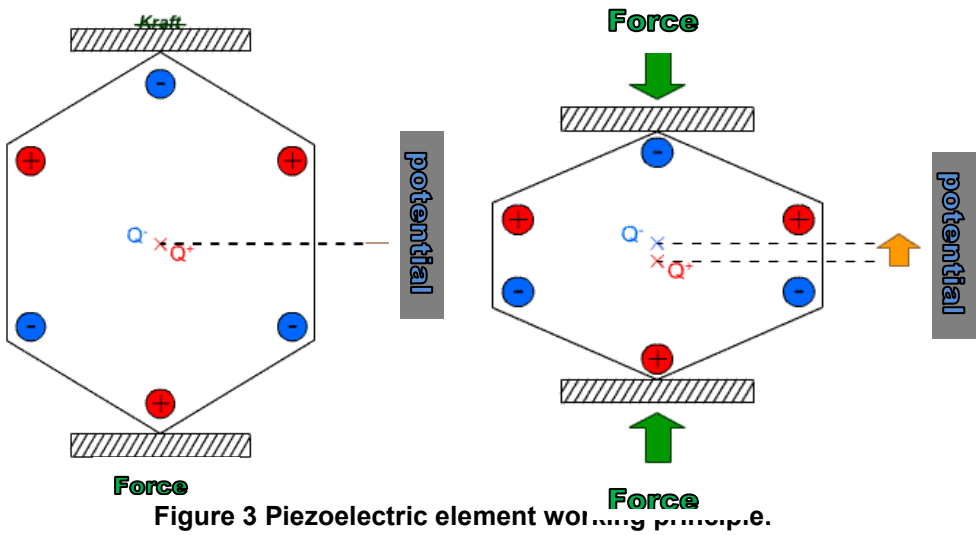


Figure 3 Piezoelectric element working principle.
Source: de.wikipedia.org
The piezoelectric sensor, in the accelerometer, changes dynamic pressure fluctuations into an electrical signal

This common approach to integrate measured acceleration over a fixed period of time into dimensionless activity counts has shown its inherent limitations, i.e. the effect of the epoch lengths on the classification of intensity or the reduced capability to recognize activity. Therefore, modern accelerometers allow the capture and storage of the raw acceleration signals. Currently, innovative research regarding improved algorithms for EE estimation and activity pattern recognition is in progress.

The validity and reliability varies depending on the accelerometer model and lies between r=0.30 to r=0.90 (30). Accelerometer device validation studies have been performed for example for the GENEA, the Lifecorder, the Caltrac, the Actigraph, the Actiwatch, the Tritrac and the Tracmor (30-32).

Depending on the device the cost may vary from 200 to 1500$. There is no risk for the participants while wearing an accelerometer. Nevertheless, those light and small sensors may influence the participants behavior in response to the fact that they know they are being studied (Hawthorne effect) (33). Altered locomotion in participants may influence the results and is therefore a contraindication for the use of accelerometers in physically disabled people (34). Recently, new accelerometer algorithms have been developed to address this issue (35).

Accelerometer counts (AC) are a product of the amplitude and the frequency of the measured acceleration signals. These parameters vary among devices and the final output from one accelerometer is not equal to the output from one another. Therefore, to compare two different devices, it was suggested to transform AC into the standard unit of acceleration which is m/s² (28). AC can be converted into other PA measures like PAEE, (30) (36) but also activity types and patterns (37) can be identified. Intensity categories including, inactivity, sedentary and vigorous behavior can be estimated. Cut-off points for intensity

categories should be deliberated as the decision to use a particular set of cut-off points has later consequences on the final results. (38-40). A disadvantage of accelerometers, worn on the waist or hip, is that they overestimate sedentary and light PA and underestimate moderate and vigorous physical activity (MVPA) that involve upper body movements but also cycling, walking uphill, climbing stairs, isometric muscle work, static PA, complex movements and running at high speeds (28, 41).

Heart rate monitoring

Heart rate monitoring provides information about the heart rate response to exercise. It is based on the physiological principle, that the heart rate increases proportional to the oxygen uptake which is positively correlated with exercise (42). Even though, there is a great variation between individuals. Multiple factors like age, sex, fitness level, weight, heart diseases, the use of beta-blockers, stress, and emotional state may modulate this relationship (43). Therefore, an individual calibration of the heart rate response to exercise is needed. This estimate indicates the threshold below which REE and above PAEE is assumed – the flex point. This method is especially valid in estimating MVPA but underestimates light activities. Therefore it was suggested to be used only for assessing time spent in MVPA (28). This might help to avoid errors that occur when measuring low intensity activity.

The reliability of heart rate monitoring was tested by Strath et al. (44). They suggested high reproducibility within subjects. Nevertheless, the validated flex point method (43, 45) still bears limitations which include the assumption that it reflects the heart rate response to exercise and no other physiological responses to external or internal stimuli like stress or caffeine intake (46). The estimation should be undertaken shortly before the heart rate measurement period to avoid changes in physical fitness, body composition or diseases, which influence the heart rate – exercise relationship.

Some devices are waterproof or fitted with Bluetooth which enables to send the recorded heart rate wireless to an external device. For the calibration a treadmill, a bike or an aerobic fitness stepper is needed which results in a cost of 50-1000$ plus the devices itself which cost up to 50$ each. In a 100 people study population this would mean 5.50$ - 150$/measurement.

Risk to participants is very low and exists only during the calibration procedure, which is a submaximal endurance test. Therefore, a physician should always be at least on call duty. The monitoring itself is non-invasive and carries no risk.

Multifunctional devices

The so called multifunctional devices are meant to combine advantages of different sensors and thereby provide better estimates. Therefore, these multifunctional devices monitor PA through at least two methods – classically heart rate and accelerometry. Most of them are able to measure even more. Electroencephalography channels, body temperature recording, galvanic skin reaction, blood pressure, respiratory screening, inclinometer (body position determination), ambient light sensor and different other possibilities that make the measurement more accurate can be integrated within one device.

Depending on the used methods the measurement can be more or less difficult. If heart rate is included the heart rate response to exercise calibration is needed. Electrodes and cables attached to the device and carrier might be unpleasant. Nevertheless, the combination of heart rate and accelerometry can lead to synergistic effects by overcoming the disadvantages of a single method. While accelerometry alone is not that reliable at measuring upper body movement like lifting weights and underestimates high speeds and cycling, heart rate devices are accurate in capturing this kind of activities. The other way around, at lower levels of intensity accelerometry is more precise than heart rate monitoring.

Monitors with ambient light sensor can be used to estimate the time spent indoor or outdoor and calculate activity patterns in the context of the place where activity is being performed. An inclinometer may be helpful by calculating time spent in different positions like: sitting, lying or standing.

The reliability and validity of some combined sensors was already tested but as there are many different usage possibilities and device models, not all of them could yet be established. Validation study examples include the combined heart rate and movement sensor Actiheart (47) and the Equivital LifeMonitor EQ02 (48).

If a heart rate monitor is included in the method than then a calibration should be performed. This might be considered a potential risk to participant. For some additional measurements cable, belts, electrodes and sensors are needed; therefore, any daily life restrictions should be accurately explained to the participant to avoid increased wearing discomfort or even breaking of the device.

Future developments in PA measurement

Emerging telecommunication technologies have become an interesting field for the use in epidemiology. Since the occurrence of the cell phone, especially the smartphone, a new possibility in measuring PA was set. These phones are equipped with GPS, video and some of them with an accelerometer of a low frequency rate. All these features combined, may provide a reliable output.

There are still very few studies which tested this method for reliability and validity. Wu et al. (49) who used a Blackberry smartphone found that for activity classification this can be a useful method, but higher sampling rates would be desirable.
Turner-McGrievy et al. (50) already used Smartphones for a PA intervention study. The participants had to download a PA monitoring application and a social network site's application to their iPhone, iPod Touch, Blackberry or Android-based phone and report their activity and weight loss to the study center.

Also easier methods like Java-based questionnaires to assess PA have been developed. They are based on the fact that a participant is able to complete them the same day the activity was performed and therefore the accuracy of this self-report is higher. Studies show that, compared to DLW and indirect calorimetry, cell phone based questionnaires are a valid measure of PAL (mean difference = 0.014, SD=0.15) (51).

3.2 Modeling and calibrating physical activity data

Studying PA and the risk of chronic diseases or the influence of PA on health related factors can be a challenge. In longitudinal studies that were set up in the nineties it was common that the only measure of PA was a self-report method. Therefore, a high risk of measurement error occurs which may alter the final analyses' results. Nowadays, statistical models can be used in order to account or adjust for the bias in PA self-report data.

Everybody lies?

Subjective measurement methods involve the highest measurement error, but various reasons explain this fact, not necessarily connected to the dishonesty of the participants. There are multiple measurement error sources that may influence the error magnitude. As discussed before, DLW is the gold standard for measuring PAEE, but one has to bear in mind that PAEE is not equal to movement. In the calculation of PAEE also body mass takes part as the higher the body mass the more energy one has to expend performing PA. For example, while jogging, a woman weighting 55 kg will have to spent approximately 385 kcal/h and a woman weighting 70 kg will spent 490 kcal (13). The amount of movement will still be the same for both women. In PAQs the amount of PA is not considered depending on the participants' weight. Furthermore, the questionnaire derived PA is a sum of activity during a "typical week" or defined period of time (typically 1 year or 4 weeks) whereas an objective PA measurement is restricted to a much shorter time period (DLW ~ maximum 2 weeks; calorimetry 24h up to 3 days; pedometer and accelerometer ~7 days). Seasonal variability may also play a crucial role in the measurement error amount (52). A repeated objective PA measure may be nearer to the real PA amount, nevertheless different sport activities can be performed during summer and winter and depending on the time point when the questionnaire or the objective measure was used to assess PA, the measured amount of PA will differ.

Last, measurement error occurs because participants do not report accurately. A questionnaire of extensive length may lead to fatigue and consequently to sloppiness in answering the questions. Social desirability may affect the answers towards a higher reported activity than it actually is ("overestimators"). On the other hand underreporting may occur in participants having difficulties in recalling the activities they engaged in or misinterpreting the PAQ questions ("underestimators"). Participants with low recreational PA will try to make up for it by over-reporting household activities that increase their questionnaire derived PA amount.

Measurement error in PA is the difference between the actual PA amount measured or estimated by an objective or subjective method and the true PA amount measured by a gold standard method. Measurement error has three main effects: it causes bias in parameter estimation for statistical models, leads to loss of power for detecting relationships among variables and it masks the features of the data, making graphical model analysis difficult (53).

Two measurement error models can be found in the literature: the **classical error model** and the **Berkson error model** (53). In the classical error model "the truth" is measured with additive error with, usually, a constant variance:

$$\boldsymbol{W_{ij} = X_i + U_{ij}} \qquad [1.1]$$

Where $\mathbf{W_{ij}}$ is a unbiased measure of $\mathbf{X_i}$. Therefore, the observation error $\mathbf{U_{ij}}$ has a mean of 0. That means that E($\mathbf{U_{ij}}$| $\mathbf{X_i}$) = 0. The error structure of the observation error could be homoscedastic or heteroscedastic. In this model it is assumed that the variability in the observed value is larger than the variability of the true value.

On the other hand, the Berkson error model turns this assumption around and implies that the true value has a higher variability than the observed value:

$$\boldsymbol{Xi = W_{ij} + U_{ij}} \qquad [1.2]$$

Where E($\mathbf{U_i}$| $\mathbf{W_i}$) = 0 (53).

In general, **regression calibration** models include Berkson error models, where the conditional distribution of **X** given the unbiased measure **W** is modeled. Additionally observed predictors **Z** (covariates) may be included into the model E(**U** | **W, Z**) = 0. The Berkson error **U** is independent of **W** E(**U** | **W**) = 0, therefore, the variance of **X** is larger than the variance of **W**.

In nonlinear cases the regression calibration can be performed using polynomials, fractional polynomials or spline regression. The nonparametric regression aims to estimate the relationship between the true measure and the proxy measure as a non-parametric function of the proxy measure.

Polynomial regression fits a nonlinear relationship between the value of $\mathbf{W_{ij}}$ and the corresponding value of $\mathbf{X_i}$, and is used to describe a nonlinear phenomenon between them. Therefore, the $\mathbf{W_{ij}}$ is being transformed into different polynomials (example: logtransformed, transformed into a quadratic term, cubic term etc.).

$$\boldsymbol{y = \beta_0 + \beta_1 x + \beta_2 x^2 + \beta_2 x^3 x} \qquad [1.3]$$

Fractional polynomials, developed by Royston and Altman (54) in 1994 is based on the fact that the exposure can be transformed with p ϵ -2, -1, -0.5, 0, 0.5, 1, 2, 3 where p=0 ln(x).

Moreover, a model with two fractional polynomials can be established and they will be tested against each other.

$$y = \beta_0 + \beta_1 x p^1 + \beta_2 x p^2 \quad [1.4]$$

where, β_0 is the intercept; if $p_1=p_2$ then the second term will be additionally logtransformed: $\beta_2 x^{p1} * \ln(x)$. Thus, the non-transformed model will be tested by a backward selection algorithm against all fractional polynomials models.

Splines are another non-parametric method. A spline is a piecewise defined function that is built by knots. Splines are usually made by a cubic function that is defined for each interval, where a smooth polynomial function builds each interval. Linear splines are also known as segmented or piecewise regression.

$$y = \begin{cases} \beta_0 + \beta_1 x & x \leq a \\ \beta_0 + \beta_1 x + \beta_2 x\,(x-a) & a < x \leq b \\ \beta_0 + \beta_1 x + \beta_2 (x-a) + \beta_3 (x-b) & b < x \end{cases} \quad [1.5]$$

Segmented regression or piecewise regression is a non-parametric method based on linear regression of the independent variable that is portioned into intervals. Segmented regression can be found in literature as a data calibration technique but is not widely used. The segments are separated by breakpoints that are determined though pre-analysis. This method is useful if the slope of the association differs between groups or values of the independent variable. For calibration, this would mean that the function $\beta_0 + \beta_1 x$ will be calculated for each segment and based on the segment in which W_{ij} lies the corresponding regression model will be applied. This method can also be performed multivariate.

The non-parametric methods can be useful in exploring the relationship nature, help in choosing the right calibration model and can be applied as a calibration method.

Sources of data for a measurement error calibration may be internal, from the same study population, or external from an independent study population. In an internal validation dataset, the measurement error calibration is easier because the used measurement techniques, covariate structure and covariate availability are the same. This allows a greater precision in estimating the measurement error. A validation data set additionally allows treating the measurement error problem as a missing data problem, and therefore, other techniques like multiple imputation may be adapted for the purpose (55). Furthermore, in an internal data set, in addition to the primary measurement **W**, instrumental variables **Z** can be added to the model as they were assessed with the same methods. Such covariates can be factors or individuals characteristics that have previously been shown to be associated with

the PA level. Sex, age, race and ethnicity, educational status or Body Mass Index (BMI) can improve the explained variance in the PA model.

3.3 Physical activity and chronic diseases: state of the art.

PA and its impact on health have been studied extensively since the 16th century. In 1584 the English physician Thomas Cogan mentioned in his book *The Haven of Health* that sedentary people appear to suffer more often from illnesses than active people. Later on, many other physicians like Ramazzini, Ricketson, Montoye, Rook demontrated in their books the increased disease burden in sedentary workers and people maintaining a sedentary lifestyle. Particularly, death causes like type 2 diabetes, coronary heart disease (CHD), stroke and cancer began to attract attention in the 20th century.

Through the years researchers successfully described in more detail the associations between PA and the risk of chronic diseases like diabetes, cancer and CHD with success. 1,513 publications occur on Pub Med for the search terms “physical activity AND cardiovascular disease (CVD)”. In terms of “physical activity AND cancer” 556 and for “physical activity AND diabetes” 653 papers, respectively (search day: 22.08.2013). Also intermediate chronic disease associated factors have been studied in the association with PA. Mostly weight and body mass connected measures of anthropometry, but also all kinds of serum or plasma markers, that might be altered by PA (56).

What is already known about PA and the effect on disease prevention can be summarized as follows (57):

- Inverse relationship with all-cause mortality
- Inverse relationship with CVD and CHD
- Inverse relationship with blood pressure and hypertension
- Inverse relationship with obesity, overweight and fat distribution
- Inverse relationship with type 2 diabetes
- Inverse relationship with colon cancer
- Positive relationship with quality of life and independent living in older persons
- Benefits in combination with secondary prevention in people after a cardiac event or cancer survivors

Beside the above mentioned relationships with disease risk, there are many other benefits from PA and the number of publications is still increasing (57):

- Increased cardiorespiratory fitness through increasing the maximal oxygen uptake
- Decreased heart rate and blood pressure, minute ventilation and myocardial oxygen coast for a given absolute submaximal intensity
- Increased capillary density in skeletal muscles

- Increased exercise threshold for the accumulation of lactate in blood and for the onset of disease symptoms
- Decreased anxiety and depression
- Increased feeling of wellbeing
- Reduced risk of falls and injuries from falls in elderly
- Increased performance in work, recreational and sport activities

3.3.1 Physical activity and the risk of type 2 diabetes

Type 2 diabetes is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (58). The WHO estimates a worldwide death rate due to diabetes of 3 million deaths each year. Diabetes increases the risk of hypertension, CHD and stroke, and causes adult blindness, leads to non-traumatic amputations and end-stage kidney failure. Type 2 diabetes is a partly genetically determined disease as family history plays an important role in disease risk. The most frequent form is type 2 diabetes which the present section also refers to.

Physical inactivity was shown to be one of the most important risk factors for diabetes besides weight gain. Randomized clinical trials confirmed that changing PA, diet, body weight or fat distribution independently decreased the risk of developing type 2 diabetes (11). The effects of PA on diabetes risk have been investigated in different studies, starting from cross-sectional, through prospective cohort studies to clinical trials – the overall consent indicates an important, inverse relationship.

It dates back to 1984 when King et al. (59) studied the type 2 diabetes prevalence in about 3000 Micronesians from the Pacific Islands and found that it was threefold higher in the urban than in rural population. This difference was not only explainable by a higher obesity prevalence but PA, which was significantly higher in the rural population.

Regular participation in PA has been shown to decrease the risk of type 2 diabetes by 30% (relative risk (RR) (95% confidence interval (CI) 0.69 (95% CI 0.58-0.83) in a systematic review of 10 prospective cohort studies (60). Big cohort studies including University of Pennsylvania Alumni Study, Nurses' Health Study, Physicians' Health Study, Aerobic Center Longitudinal Study and the Women's Health Initiative Study have shown a greater risk for developing diabetes in physically inactive individuals compared to active, independently of known risk factors (61-65). The highest RR was reported in the Nurses' Health Study after 16 years of follow up, where compared to active (>21.8 MET-hours/week), normal-weight women (BMI<25 kg/m²) the RR for inactive (<2.1 MET-hours/week), obese (BMI>30 kg/m²) women was 16.8 (95% CI 14.0-20.0)(63).

The Finnish Diabetes Prevention Programs, being a randomized controlled trial, also confirmed the benefits of increased PA and simultaneous weight loss in reducing the progression of impaired glucose tolerance to type 2 diabetes (66). Even more encouraging

results were produced by the U.S. Diabetes Prevention Program, where 3,234 adults were assigned to three diabetes preventing groups including a placebo group. After three years the prevalence of the metabolic syndrome, which was 55% at baseline, increased to 61% in the placebo group, remained constant (54%) in the metformin group and decreased to 43% in the diet + exercise group (67).

There is high conformity supporting the hypothesis that PA reduces the risk of type 2 diabetes. Furthermore, biological plausibility provides a framework for this scientific evidence. Lowered fat mass in physically active people may explain part of the effect of PA, but during exercise also glucose uptake in the muscles, glycogenolysis and gluconeogenesis, and lipolysis of free fatty acids from adipose cells are increased (11). Moreover, there is a decreased insulin secretion due to increased growth hormone and increased cortisol from the adrenal cortex, increased epinephrine secretion and increased glucagon (11).

3.3.2 Physical activity and risk of coronary heart disease

CHD belongs to a group of disorders of the heart and blood vessels and is characterized by narrowing of the small blood vessels that supply blood and oxygen to the heart. The WHO estimated that CVD including CHD causes more than 50% of all deaths across the European Region (68).

In the early nineteen-fifties, Morris et al. (69) compared the prevalence of CHD between bus drivers and conductors, and between telephonists and postmen (Figure 4). Middle aged men and women in the physically active jobs had a lower incidence of CHD than those in the physically inactive job segments. More important, the disease was not so severe in physically active workers, tending to present first as relatively benign forms, and to have a smaller early case fatality and lower early mortality rate (69).

Since then, the impact of PA on CVD and CHD risk was widely studied not only in occupational but also in recreational settings. The well controlled Harvard Alumni Health Study investigated the relationship between questionnaire derived PAEE and CHD risk in 7,307 male alumni of Harvard University and found a linearly decreasing risk of CHD from 1.0 (1000 kcal/week) to 0.62 (≥4000 kcal/week) in 5 PAEE categories (p-

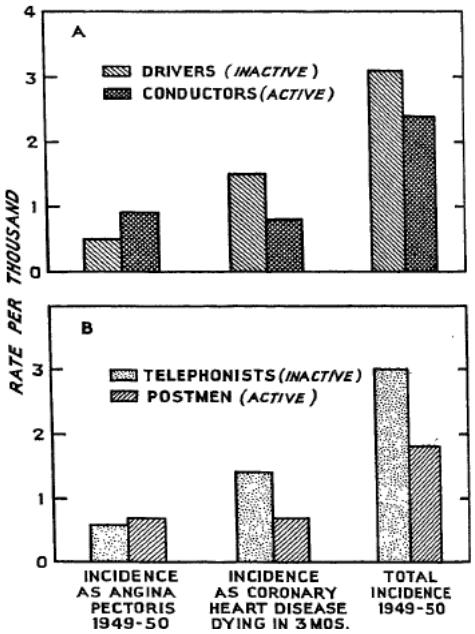


Figure 4 First clinical episodes of CHD in drivers, conductors and telephonists, postmen (adapted from Morris et al. (69))

trend=0.046) regardless of other CHD risk factors (70). Likewise, investigators of the Framingham Heart study found an inverse relationship between PA and CHD risk in men (71). However, this finding could not be confirmed in women, possibly due to low power. The Nurses' Health Study provided this risk estimation by analyzing data from 72,488 female nurses (72). The standard CHD risk factors adjusted RR for CHD were decreasing across quintiles of PAEE with a RR of 0.66 (95% CI 0.51, 0.86) in the highest quintile compared to the lowest quintile. Paffenbarger et al. (73) estimated the population attributable risks (an estimate of the reduction in disease rate that might occur if all individuals carrying a specific risk factor eliminate it) based on the Harvard Alumni Health Study population. The population attributable risk for CHD mortality and MVPA equaled 14% thus, the CHD mortality rate could have been reduced by 14% if all participants of the Harvard Alumni Health Study sample had taken up MVPA (defined as >4.5 MET). This dimension is comparable with established risk factors including overweight (11%), cigarette smoking (13%) and hypertension (20%) (73).
The strength of evidence is sufficient to state that PA is associated with a lower CHD risk. The causality of these relationships may also be pointed out by biological plausibility. PA is associated with decreased body weight, blood pressure, improved glucose tolerance, higher HDL level, lowered inflammation and higher cardiorespiratory fitness, which are protective factors for CVD (11).

3.3.3 Physical activity and risk of stroke

According to the WHO, a stroke is a disease caused by the interruption of the blood supply in the brain, usually because a blood vessel bursts or is blocked by a clot. Thereby the supply of oxygen and nutrients is interrupted, causing damage to the brain tissue (74).
Different from CHD and diabetes, where the evidence was strongly pointing to the inverse relationship, in terms of stroke previous studies still show conflicting results. This may be due to different pathophysiological mechanisms of stroke: embolic, thrombotic and lacunar which are often studied together.
A meta-analysis published in 2004 studied 31 publications on PA and risk of stroke (24 cohort and 7 case-control studies) (75). Occupational activity and leisure time PA have been investigated separately in the majority of the included publications. Therefore, the pooled analysis was presented for both, occupational and leisure time PA. For occupational activity it was shown that active people compared to inactive had a RR of 0.74 (0.49;1.12) for total stroke, 0.31 (0.13;0.76) for hemorrhagic stroke and 0.57 (0.43;0.77) for ischemic stroke. Moderately active had compared to inactive workers a RR of 0.64 (0.48;0.87) for total stroke, 0.45 (0.14;1.39) for hemorrhagic stroke and 0.67 (0.35;1.29) for ischemic stroke indicating risk reducing effect of occupational PA but the risk estimates were rather imprecise. More convincing results were shown for leisure time PA where active compared to inactive individuals had a RR of 0.78 (0.71;0.85) for total stroke, 0.74 (0.57; 0.96) for hemorrhagic

stroke and 0.79 (0.69;0.96) for ischemic stroke. Moderately active compared to active participants had a RR of 0.85 (0.78;0.93) for total stroke, 0.76 (0.55;1.05) for hemorrhagic stroke and 0.83 (0.64;1.09) for ischemic stroke (75).

Recently, in EPIC Spain, where the PA measurement was based on the EPIC-PAQ and MET/h/ week were calculated, only moderate intensity PA was inversely associated with risk of stroke 0.45 (0.22; 0.90) in women. No significant associations for men were observed (76).

Although, the evidence for an inverse association between PA and risk of stroke is less strong than for type 2 diabetes and CHD, the direction of the association points towards an inverse relationship, which would also be biologically plausible. The pathophysiology of ischemic stroke is similar to that of atherosclerosis and the development of arterial thrombosis is similar to that of CHD. Therefore, the positive influence of PA on blood lipids, cholesterol and increasing high density lipoprotein might inhibit the development of ischemic stroke (11).

3.3.4 Physical activity and risk of cancer

Uncontrolled growth is the main characteristic for abnormal cells that become a tumor and are defined as cancer. The origin site of a cancer determines his name, which means that cancers arising from epithelial cells are called carcinoma and those from connective tissue sarcoma. Cancer stages I – IV define how advanced the cancer is spread across the primary and neighboring tissues (11). The most common and most often studied cancers are located in the tissues of the: lung, breast, ovary, prostate, colon and rectum, liver, pancreas, leukemia, esophagus, skin, non-Hodgkin lymphoma, brain and nerves, kidney and urinary bladder. The different etiology of those cancers necessitates, that their associations with PA are studied separately. Strong evidence is available on a protective effect of PA on risk of colon cancer and breast cancer supporting that at least moderate activity (>4-5 MET) reduces the risk (77). For lung and endometrial cancer the data is more limited and for rectal and prostate cancer still scarce or does not support a protective effect.

Bernardino Ramazzini (1633-1714) was one of the first to discover the cancer preventive impact of PA. In his work *De Morbis Artificum Diatriba (The disease of workers, Modena, 1700)* he characterized the health hazards of more than 50 occupations, including runners and athletes. Based on his results, he was convinced that PA should be prescribed to sedentary workers in order to prevent diseases like cancer (78).

Wolin et al. (79) examined 52 studies on PA and risk of colon cancer and observed an inverse relationship across the studies. Compared to the inactive, the most active individuals had a 24% lower risk of colon cancer RR=0.76 (0.72;0.81). The relationship was similar when stratified by sex. Case-control studies showed stronger associations of RR 0.69 (0.65;0.74). In the whole EPIC cohort an inverse relationship particularly for the risk of right colon cancer was found with a RR of 0.65 (0.43;1.00) (80). For overall colon cancer the

relationship was also inverse and with a similar wide confidence interval. No relationship with rectal cancer could be identified.

In a systematic review including case-control and cohort studies PA was associated with a risk reduction of 20-80% for postmenopausal breast cancer. A trend analysis of 17 studies indicated a dose-response relationship of a 6% decrease of breast cancer risk for each additional hour of PA per week. In EPIC no significant linear associations were found for PA and risk of breast cancer when the Total Physical Activity Index was used. An inverse relationship was found for multivariate adjusted household activities with a RR of 0.71 (0.55;0.90) for premenopausal and RR of 0.81 (0.70;0.93) for postmenopausal women. The hormone receptor status seems to be a factor that interacts with PA. In Estrogen receptor +/Progesterone receptor + breast tumors PA had a stronger inverse relationship than in other tumor types (81). For risk of in-situ breast cancer the EPIC study could not find any associations with PA (82).

Biological plausibility of the relationship between PA and risk of colon cancer can be seen in different mechanisms. A shortened gastrointestinal transit time of active people may be one approach, but also the reduction of systemic inflammation or increased levels of Prostaglandin F (that increases gut motility) may be an important issues (11). Since breast cancer is highly hormone-dependent, it was proposed that PA might protect against breast cancer by reducing the luteal phase exposure of women (high levels of estrogen and progesterone phase) or lengthening the menstrual cycle and delaying the age at menarche (83).

3.4 Public health relevance

Physical inactivity has been identified as the 4th leading risk factor for mortality and approximately 3.2 million deaths (6%) each year are attributable to physical inactivity. Physical inactivity is estimated as being the principal cause of approximately 21–25% of breast and colon cancer burden, 27% of diabetes and approximately 30% of ischemic heart disease burden (84).

The overall conclusion of previous studies is consistent, although not unanimous. PA reduces the risk of most chronic diseases. Nevertheless, most of the studies investigating the relationship between PA and risk of chronic diseases have a major limitation: they used subjective methods to assess PA, i.e. questionnaires. Different dimensions have been considered and different measures for PA applied. Some investigations considered PA intensity, concentrating on the estimation of MET/h spent in a timeframe, some studies adressed estimated EE in kcal or kJ and some used indices that already categorize participants into active or inactive. Taking into account that the measurement error in PA questionnaires is very high, one should consider the consequences for risk estimation. Thereby, it is possible that some of the studied traits have been under or overestimated and linear or non-linear effects were missed or mistakenly interpreted as truth. Some relationships (especially if small) have been missed due to poor PA measurement and consequently lower statistical power. Ferrari et al. (85) already pointed out the importance of measurement error correction:

"These results suggest that the overall level of attenuation may be greater than previously expected, which confirms the importance of estimating the attenuation factors accurately because quantification of the impact of physical activity on public health outcomes will be directly affected by such attenuation." (85).

It is a public health interest to study the protective effect of PA on risk of chronic diseases on data that is not limited by large measurement error, based on objective measurements or at least with calibrated data. Therefore, by accomplishing the aims of this thesis an important step towards a better understanding of the relationship between PA and risk of chronic diseases will be made. This may eventually have public health implications to generate improved recommendations for chronic disease prevention through PA.

4. Material and methods

4.1 Study population

The EPIC study is one of the largest studies of diet and health ever conducted with over half a million (520,000) participants in ten European countries: Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom (Figure 5) (86).

The German EPIC centers Potsdam and Heidelberg recruited 53,088 participants from the surrounding general population from 1994 to 1998 (87).

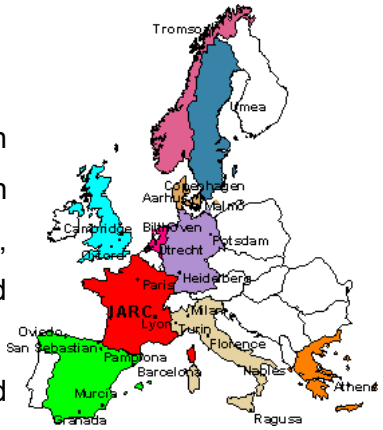


Figure 5 European Prospective Investigation into Cancer and Nutrition study centers

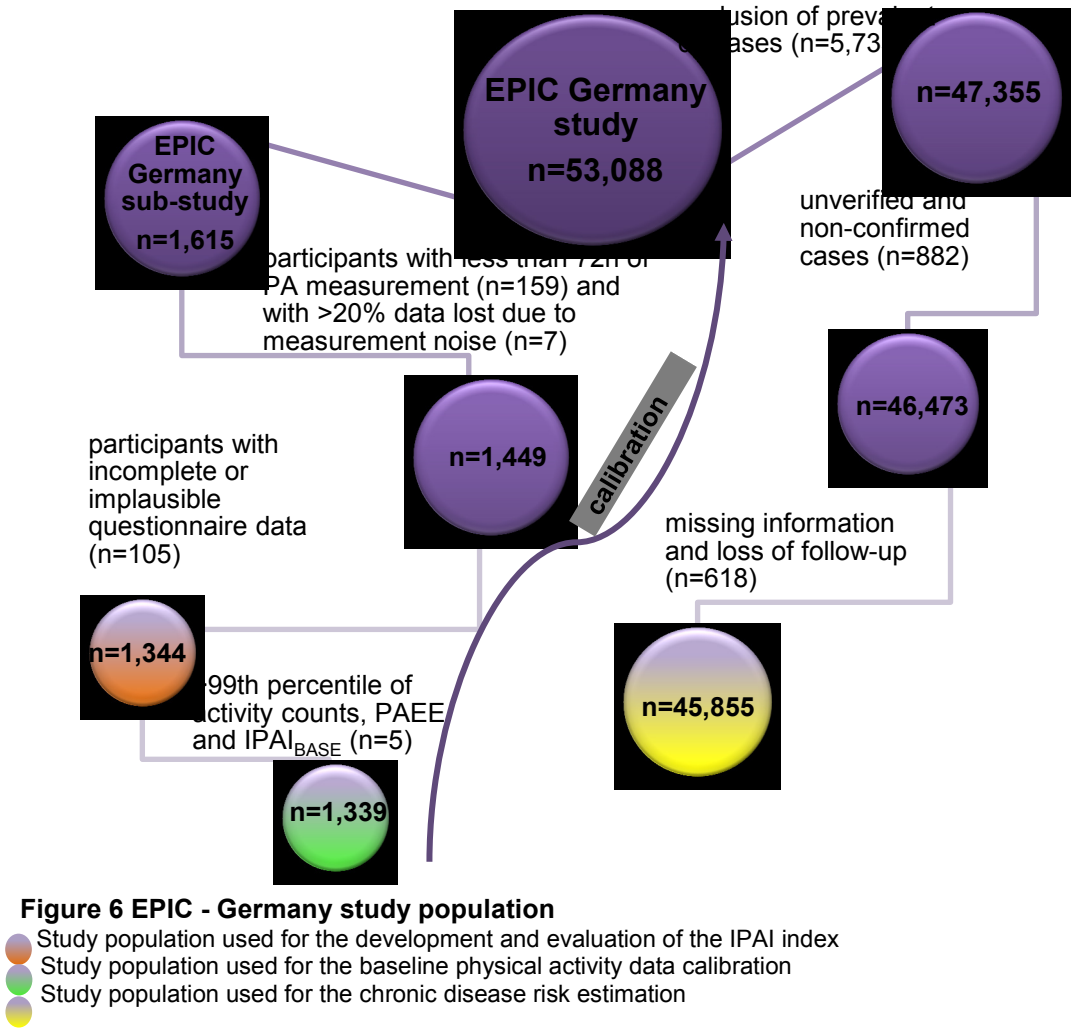


Figure 6 EPIC - Germany study population

Study population used for the development and evaluation of the IPAI index
Study population used for the baseline physical activity data calibration
Study population used for the chronic disease risk estimation

4.1.1 The EPIC Germany Study

At the German study centers Potsdam and Heidelberg, a study population of 27,548 (16,644 men and 10,904 women) and 25,440 participants (11,928 men and 13,612 women), respectively, were recruited using general population registries. The participants were initially 35-65 years old (87).

Physical examinations including standardized measurements of blood pressure and anthropometrics at recruitment were performed. Self-administered questionnaires and computer-guided interviews were applied to assess diet, lifestyle and prevalent comorbidities (87, 88). All participants gave written informed consent and the study's ethic approval was obtained from the Ethics Committee of Medical Society of the federal state of Brandenburg (Potsdam) and the medical faculty of the University of Heidelberg, respectively.

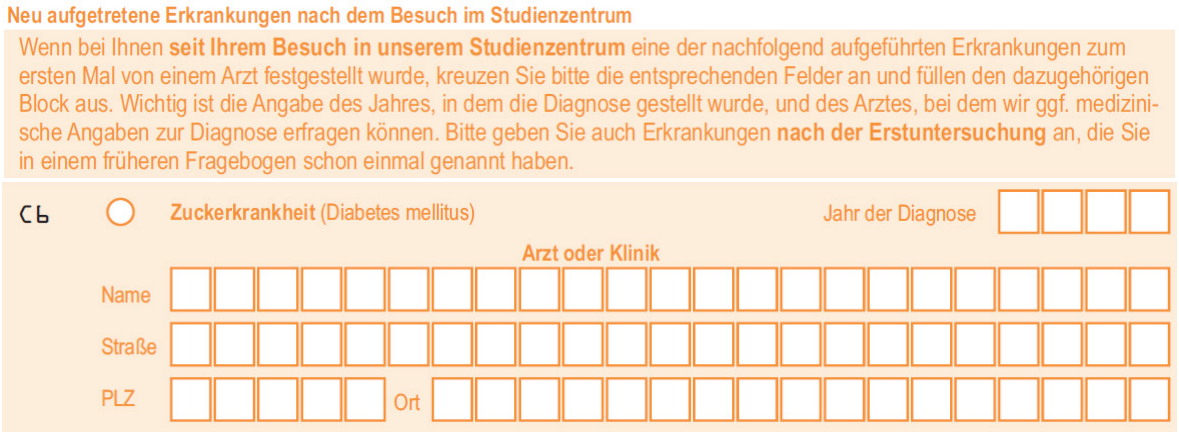
For the risk analysis participants with prevalent chronic diseases (5,733 subjects), unverified, non-confirmed cases (882 subjects), with missing information on PA (10 subjects) and 608 subjects without follow-up data were excluded (Figure 6). Finally, **45,855** participants entered the analyses including 4,508 chronic disease cases of which

- 1,605 incident type 2 diabetes cases
- 371 incident MI cases
- 342 incident stroke cases
- 2,190 incident cancer cases

occurred during a mean follow-up time of 7.76 years (Potsdam: 7.8 years, Heidelberg: 7.7 years). Only the first events were considered for our analyses.

Ascertainment of diseases

The procedures of case ascertainment in the two cohorts have already been described in detail (89, 90). Briefly, potential incident cases were identified either by self-report or death certificate. Biennially, the subjects were asked about several newly diagnosed diseases via postal questionnaires (Figure 7). Reported chronic disease outcomes (type 2 diabetes, myocardial infarction, stroke and cancer) were verified by reviews of medical records and death certificates or by contacting the patients' attending physician. The International Classification of Diseases (10th revision, ICD-10) was used to code all verified incident cases.


Neu aufgetretene Erkrankungen nach dem Besuch im Studienzentrum

Wenn bei Ihnen **seit Ihrem Besuch in unserem Studienzentrum** eine der nachfolgend aufgeführten Erkrankungen zum ersten Mal von einem Arzt festgestellt wurde, kreuzen Sie bitte die entsprechenden Felder an und füllen den dazugehörigen Block aus. Wichtig ist die Angabe des Jahres, in dem die Diagnose gestellt wurde, und des Arztes, bei dem wir ggf. medizinische Angaben zur Diagnose erfragen können. Bitte geben Sie auch Erkrankungen **nach der Erstuntersuchung** an, die Sie in einem früheren Fragebogen schon einmal genannt haben.

CB ○ **Zuckerkrankheit** (Diabetes mellitus) Jahr der Diagnose

Arzt oder Klinik

Name

Straße

PLZ Ort

Figure 7 Assessment of incident diseases in the third follow-up questionnaire (example: type 2 diabetes)

4.1.2 The EPIC sub-study

In the two German EPIC centers (Potsdam and Heidelberg) a sub-sample of 3,766 participants was randomly selected from the original cohort (Figure 6). Among those 1,615 agreed to participate in the sub-study (~3% of the original cohort). The selection process included age and sex information in order to equally distribute the participants over the age and sex groups. Ethical approval was obtained from the local ethics committees in Potsdam and Heidelberg. All participants signed an informed consent prior to their inclusion into the study. Participants completed an extensive PAQ and were also fitted with a combined heart rate and movement monitor that objectively measured PA continuously over a 7-day period. A simple step test was used for individual calibration of the heart rate response to exercise. Exclusion criteria for the PA part were physical impairment and plaster allergy to avoid skin reactions to the ECG electrodes. Step test exclusion criteria were severe cardiologic illness (i.e. aortic aneurysm, recent myocardial infarction, heart failure, myocarditis, cardiac dysrhythmia, cardiomyopathy, stroke, hypertension and angina pectoris), the use of more than ½ of the maximum beta-blockers dose/day or physical disability preventing participants to walk unaided for a minimum of 10 minutes. If a smaller dose of beta blockers was used the participant was classified for a shorter version of the step test.

Participants that had less than 72h of long-term PA measurement (n=159 participants) or more than 20% of the measured data was lost due to signal noise (n=7 participants) were excluded. Furthermore, participants with incomplete or implausible questionnaire data (n=105 participants) were excluded. **1,344** participants were available for analysis. A split-sample internal validation was performed and therefore the sample was divided. The training sample consisted of the first 433 consecutive participants (32%) (206 from Heidelberg and 227 from Potsdam) that attended the study centers. The validation sample included the remaining 911 (68%) participants (482 from Heidelberg and 429 from Potsdam).

For the calibration study participants with objectively measured PA above the 99th percentile for AC (>85.5 counts/min), PAEE (>19.28 kJ/kg/day) and questionnaire derived $IPAI_{BASE}$>1.76 (5 participants) were further excluded, leading to an internal validation dataset of **1,339** participants.

4.2 Physical activity measurement

4.2.1 Physical Activity Questionnaires

In the sub-study, several PAQs were used. First, the recently validated RPAQ was applied (2). The included questions ask about PA patterns in and around the house, travel to work, activity at work and recreational activities during the last four weeks (4). Second the EPIC-PAQ 2 was applied (5), which comprises questions about PA during the last year. The employment status, participation in several activities (walking, cycling, do-it-yourself activities, gardening, sports and household chores) separated for summer and winter, participation in vigorous non-occupational activities, and the number of stairs climbed per day are the main PA dimensions of the questionnaire (91). The Total PA Index and the Cambridge Index can be derived from both questionnaires to assign the participants to a PA level.

The third questionnaire applied was the short ALPHA environmental questionnaire (92) which contains ten questions about the residential environment. Furthermore, three questions about the interest in sport activities and reasons of performing or not performing them were asked.

4.2.2 The Actiheart

A validated combined accelerometer and heart rate monitoring device (Actiheart, CamNtech, Cambridge, UK) was used, which was attached to the chest via two standard electrocardiogram electrodes (Figure 8) (47).

Figure 8 The Actiheart heart-rate and acceleration sensor

Source: http://www.camntech.com/products/actiheart/actiheart-overview

The acceleration is measured by a piezoelectric element with a dynamic range of 1-7 Hz (3dB) and a sampling frequency of 32 Hz. The Actiheart processes the raw acceleration

signals into a number of variables among others: AC, TEE, PAEE, physical activity level (PAL = (TEE/Basal Metablic Rate)) and time spent in different activity intensity categories.

Before the Actiheart was initialized for long-term recording a simple step test was performed in order to individually calibrate the device to the participant. Those were asked to step up and down a 20 cm step following a voice that progressively speeded up from 60 steps/minute to 132 steps/minute across the 8 minutes of the test. The test was followed by a 2 minute recovery phase. When the participants' heart rate exceeded 85% of his/her age-dependent maximal heart rate or subjective, severe exhaustion symptoms occurred, the test was stopped. A group calibration model for the relationship between heart rate and workload was applied if a participant was excluded from the step test or <4min of step test data were available. Otherwise the individual calibration data was used (93).

After calibration the participants were requested to wear the device continuously for seven days and to send it back afterwards. Data collected by the sensor were trimmed in each center applying the start and end time point and calculating the mean sleeping heart rate from the mean heart rates from every night period (00:00-06:00) during the measurement. Step test data was centrally cleaned in Potsdam and the appropriate calibration model, was applied, as described above. AC [counts/min/day], PAEE [kJ/kg/day], MVPA [h/day] (>3 MET), time spent sedentary (<1.5 MET) [h/day] and the PAL were calculated for each individual by the Actiheart software.

4.3 Covariates

Covariates for chronic disease risk estimation were collected at baseline. Potential confounders were identified by literature research. The following covariates were taken into consideration:

Non-modifiable: Age and sex.

Anthropometry: BMI, weight, height, waist and hip circumference were measured in the study center by trained staff. BMI was calculated as the weight divided height squared. For the calibration BMI categories according to WHO were set up (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0) (94).

Nutrition: Fruit intake (<50 g/day, ≥50<100 g/day, ≥100<150 g/day ≥150 g/day), vegetable intake (<100 g/day, ≥100<200 g/day, ≥200<300 g/day ≥300 g/day), meat intake (<30 g/day, ≥30<60 g/day, ≥60<90 g/day ≥90 g/day), coffee intake (<1 cup/day, ≥1<2 cups/day, ≥2<3 cups/day, ≥4<5 cups/day, >5 cups/day), energy intake (kcal/day). Nutritional variables were assessed by a semi-quantitative food frequency and portion size questionnaire.

Lifestyle factors, education: Educational attainment (none, primary school completed, technical/professional school, secondary school, higher education), alcohol intake (<5 g/day, ≥5<10 g/day, ≥10<15 g/day, ≥15<20 g/day ≥20 g/day), vitamin and mineral supplementation (yes/no), smoking status (never, former smoker, smoker). Lifestyle variables and education were assessed by questionnaire.

Health assessment: Hypertension (yes/no) was assessed by self-report.

Other: Life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied) was measured by self-report. Cardiorespiratory fitness was not assessed at baseline.

Confounder selection for the Cox proportional hazards regression was performed according to the Directed Acyclic Graph (DAG) theory using the DAGitty v2.0 software (95). Those causal graphs visually summarize relations among variables which can be translated into structural equations. Each arrow pointing from one variable to another represents an investigator's assumption about causal relations among them. The DAG theory implies that the diagram must be directed (each arrow points in only one direction) and acyclic (no closed loops). This method allowed estimating the **total effect** (the main model in this analysis), which describes the sum of direct and indirect effects (including mediators) of the exposure on the outcome variable. The so called **direct effect** adjustment set was also determined, which is a procedure allowing adjustment for intermediates to estimate the effect of exposure on outcome that is not depending on mediator variables. As a mediator variable may modify

the magnitude of the direct effect it is ambiguous that indirect effects overlap with the direct effects (96).

For each disease outcome a DAG was modeled according to the direction of an association between the exposure and outcome variable and the potential confounders. Literature review and internal department discussions were used to determine the direction of each arrow pointing from one variable to another. After the DAG's were drawn causal paths (paths directed from the exposure through other covariates to the outcome) were identified and minimally sufficient adjustment sets for both the total effect and the direct effect were determined. The modeled DAG's are presented in Figure 9a-e.

- Chronic diseases:

Total effect minimally sufficient adjustment set: age, sex, educational attainment.

Direct effect minimally sufficient adjustment set: not possible due to the not observed variable: fitness. Possible adjustment set including fitness:

age, sex, anthropometry, fruits, vegetables, meat intake, dietary supplements, alcohol, smoking, life satisfaction, fitness and hypertension.

- Type 2 diabetes:

Total effect minimally sufficient adjustment set: age, sex, educational attainment.

Direct effect minimally sufficient adjustment set age, sex, anthropometry, fruits, vegetables, red meat intake, dietary supplements, alcohol, smoking, and hypertension.

- Myocardial infarction:

Total effect minimally sufficient adjustment set: age, sex, educational attainment.

Direct effect minimally sufficient adjustment set: not possible due to the not observed variable: fitness. Possible adjustment sets including fitness:

age, sex, anthropometry, fruits , vegetables, meat intake, alcohol, smoking, chronic stress, fitness and hypertension.

age, sex, educational attainment, anthropometry, fruits, vegetables, meat intake, smoking, life satisfaction, fitness and hypertension.

- Stroke:

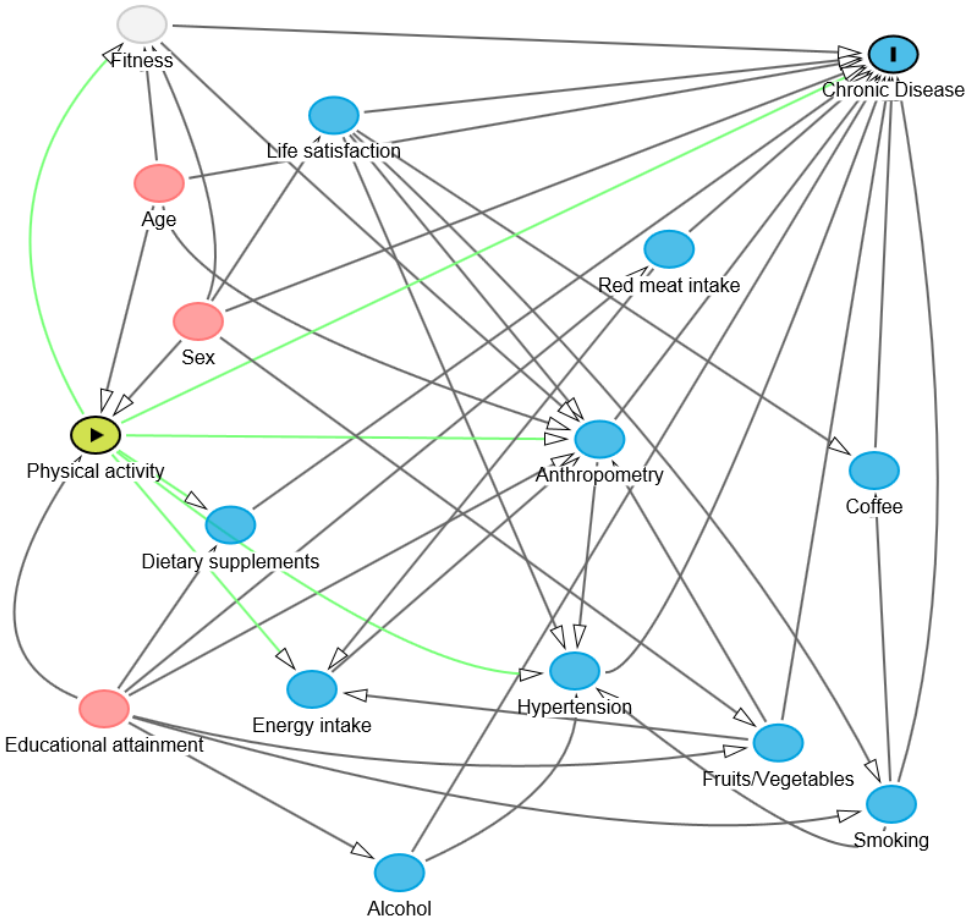
Total effect minimally sufficient adjustment set: age, sex, educational attainment.

Direct effect minimally sufficient adjustment set: age, sex, anthropometry, fruits, vegetables, meat intake, alcohol, smoking, life satisfaction and hypertension.

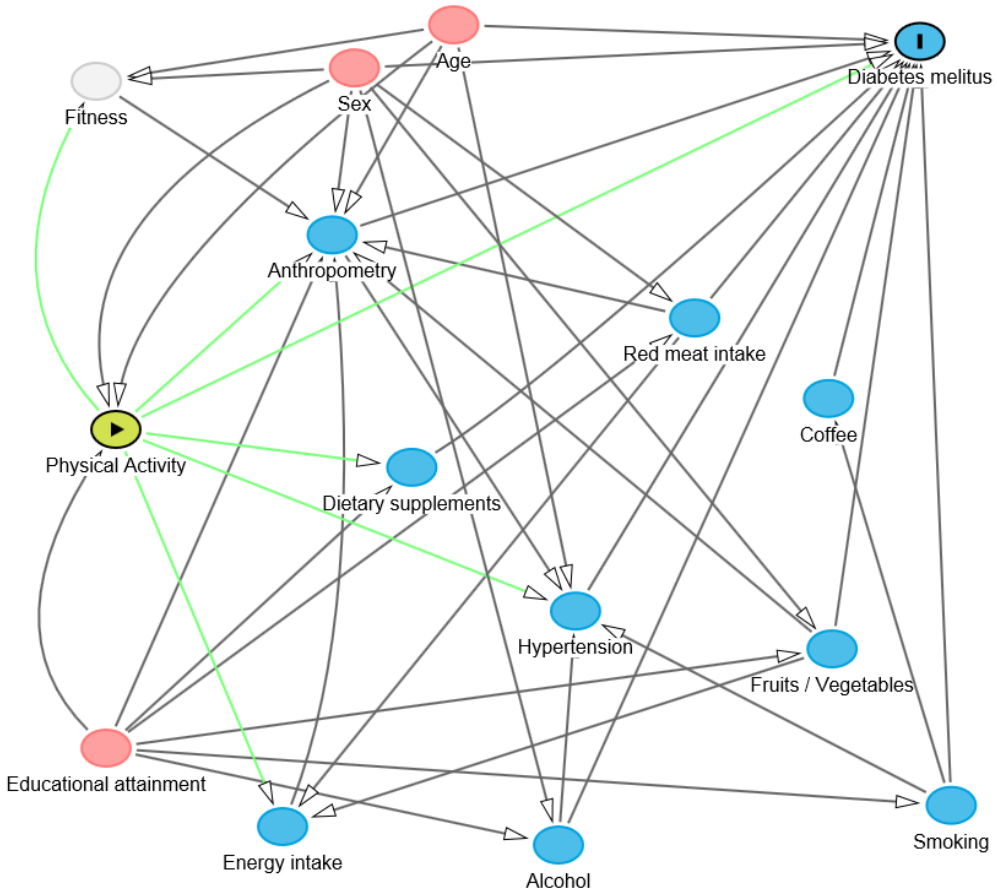
- Cancer:

Total effect minimally sufficient adjustment set: age, sex, educational attainment.

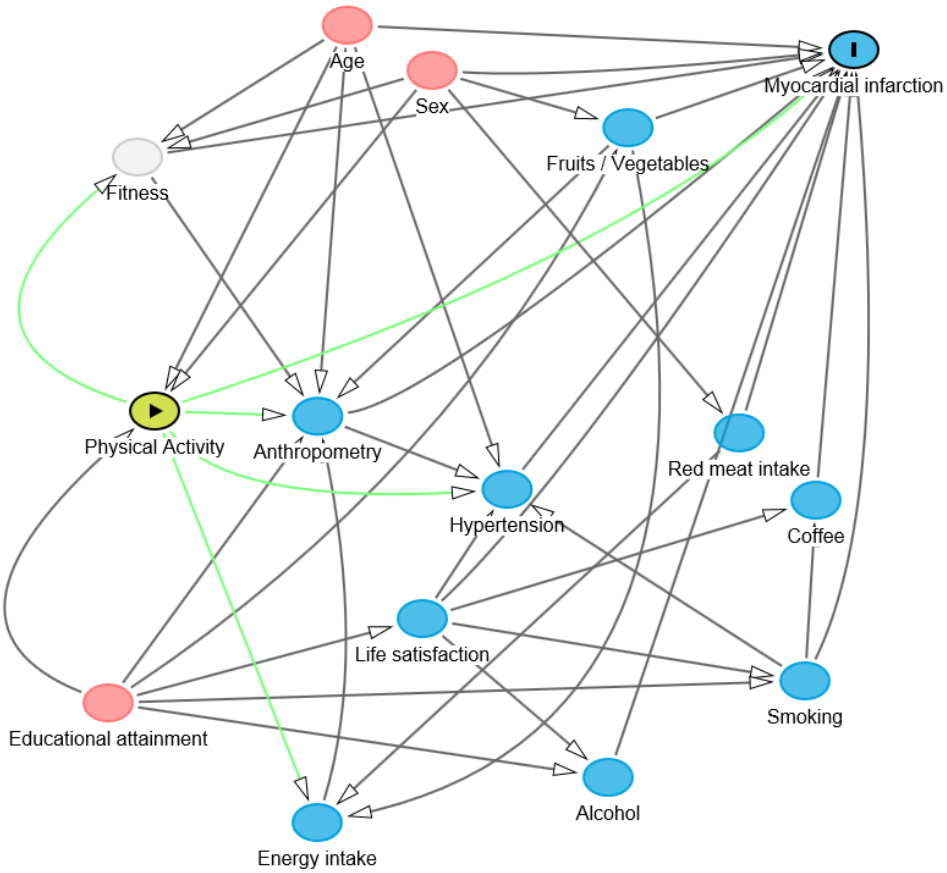
Direct effect minimally sufficient adjustment set: age, sex, anthropometry, fruits, vegetables, meat intake, dietary supplements, alcohol, smoking, life satisfaction and hypertension.



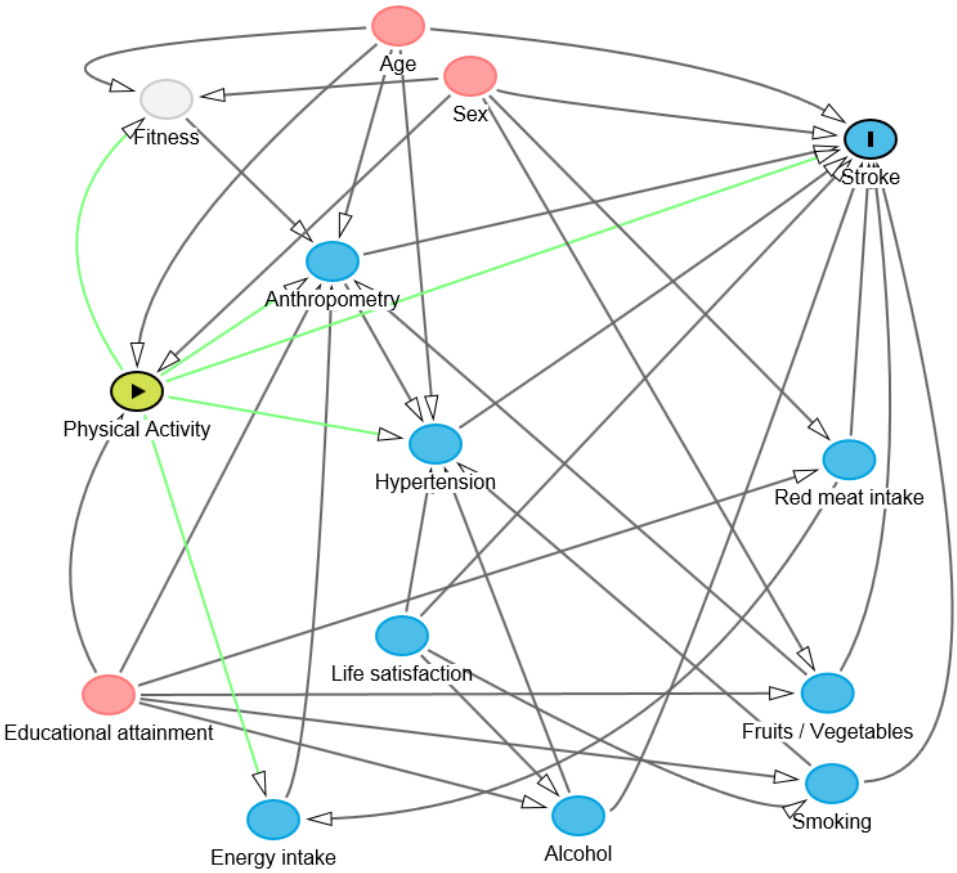
a) Directed acyclic graph for the association between physical activity and chronic diseases



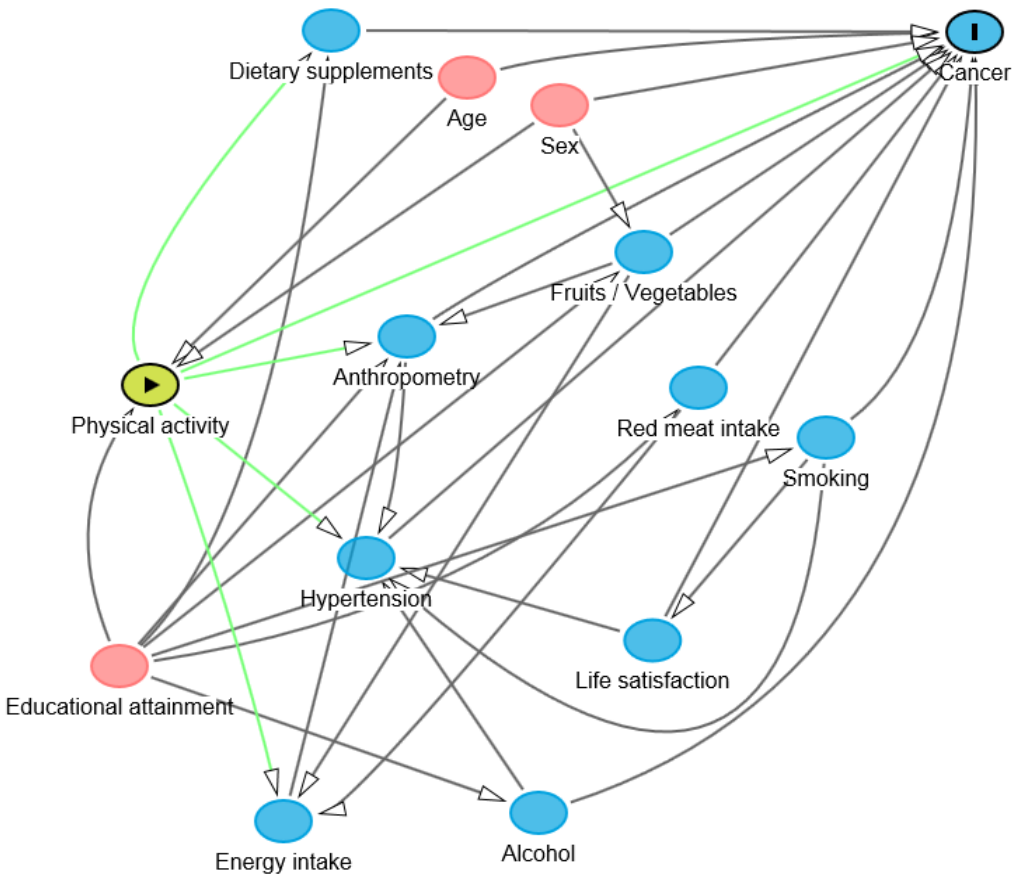
b) Directed acyclic graph for the association between physical activity and type 2 diabetes.



c) Directed acyclic graph for the association between physical activity and myocardial infarction.



d) Directed acyclic graph for the association between physical activity and stroke.



e) Directed acyclic graph for the association between physical activity and cancer.

Figure 9 (a-e) Directed acyclic graph for the association between physical activity and major chronic diseases

* Green lines indicate causal paths, black lines indicate biasing paths. Blue circles indicate ancestors of outcome, red circles indicate ancestors of exposure, white circles are latent (unobserved) variables.

4.4 Statistical methods

4.4.1 Improved Physical Activity Index development and evaluation methods

First, a t-test and a chi-squared test were applied to test for significant differences between the training sample and the validation sample.

The Total Physical Activity Index and the Cambridge Index were calculated according to the recommendations (3, 97). Briefly, for the Total Physical Activity Index the time spent in different activities multiplied by their assigned MET values was summed up: for walking and housework (3.0 MET), for gardening (4.0 MET), for home repair (do-it-yourself activities) (4.5 MET), for cycling and sports (6 MET) and for stair climbing (8.0 MET). The level of occupational activity (sedentary/standing/manual/heavy manual/non-working) was cross-tabulated with combined recreational and household activities (in sex-specific quartiles of MET-hours/week) (Table 1). The Cambridge Index was generated by using the sum of average hours spent in cycling and sport during summer and winter and was also cross tabulated with the occupational activity (Table 2).

Table 1 Total Physical Activity Index cross tabulation between recreational and household activities (MET-hours/week) and occupational activity.

Occupational Activity	Recreational and household activity (MET-hours/week)			
	Low	Medium	High	Very High
Sedentary	Inactive	Inactive	Moderately inactive	Moderately active
Standing	Moderately inactive	Moderately inactive	Moderately active	Active
Manual	Moderately active	Moderately active	Active	Active
Heavy manual	Moderately active	Moderately active	Active	Active
Unemployed	Moderately inactive	Moderately inactive	Moderately active	Moderately active
Unknown/Missing	Inactive	Moderately inactive	Moderately inactive	Moderately active

Table 2 Cambridge Index cross tabulation between hours spent in sports and cycling, and occupational activity.

Occupational Activity	Sport and cycling (h/week)			
	No activity	≤3,5	>3,5 to ≤7,0	>7,0
Sedentary	Inactive	Moderately inactive	Moderately active	Active
Standing	Moderately inactive	Moderately active	Active	Active
Manual	Moderately active	Active	Active	Active
Heavy manual	Active	Active	Active	Active
Unemployed/Missing	Inactive	Moderately inactive	Moderately active	Active

The selection of the questions for the IPAI development was performed in the following steps.

1. Initially, the set of RPAQ questions about the frequency and duration of sport activities, the EPIC-PAQ2 questions about the intensity of sport activities, and questions about the residency area from the ALPHA questionnaire were related to the objectively measured activity variables AC, PAEE, and PAL. As some variables were not normally distributed, Spearman correlation analyses were performed;
2. Subsequently, different approaches were used to reduce the 121 different sport variables to a number of meaningful scores of sport activity by:
   - summing up all sport frequency questions which were positively or negatively correlated with at least two of the objective activity variables with $r \geq \pm 0.05$ (Sport_score);
   - summing up all sport duration questions which were positively correlated (Week4_sport); summing up all sport intensity questions and multiplying them by their corresponding MET value according to Ainsworth (13) (MET_sport);
   - summing up all positively correlated residency area variables and subtracting the negatively correlated variables (residency area);

   Furthermore, scores were assigned for questions concerning television viewing and computer use frequency (television viewing (TV) and personal computer (PC) use categories: **1:** never; **2:** ≤ 1 h/day; **3:** 1-2 h/day; **4:** 2-3 h/day; **5:** 3-4 h/day; **6:** > 4 h/day) and weighted for number of weekdays (5/7 days = 0.71) and weekend days (2/7 days = 0.29):

   TV score = (TV weekday day + TV weekday evening) * **0.71** + (TV weekend day + TV weekend evening) * **0.29**; [1.6]

   PC score = (PC weekday day + PC weekday evening) * **0.71** + (PC weekend day + PC weekend evening) * **0.29**; [1.7]

3. In a next step, again Spearman correlation analyses with AC, PAEE and PAL were performed including the newly generated scores. The obtained correlation matrix allowed choosing one of the previously built sport variables with the highest correlation coefficient for AC and also comparing the newly built television and computer use scores with each of the single television and computer use questions. This approach resulted in choosing the highest correlated sport variable, television and computer use variable for further analyses.

Linear regression with stepwise variable selection including the new sport, TV/PC and residency area variables and all remaining EPIC-PAQ2, RPAQ questions was used to select

the final set of variables for the index that explains the most variance in AC ($p<0.05$). For the chosen variables descriptive distribution characteristics were calculated. In order to make the variables equally contributing to the final score of the index, they were standardized by their respective range in the index formula. Therefore, the variable value was divided by the variable range.

$$\text{Variable}_{value} / \text{Variable}_{range}$$

The IPAI score was calculated for every participant and ascribed 5 IPAI activity levels: inactive (≤20th percentile), moderately inactive (20th – 40th percentile), moderately active (40th – 60th percentile), active (60th – 90th percentile) and very active (>90th percentile).

The last step in the development process was comparing the new index with the two existing indices (Cambridge Index and Total Physical Activity Index). This was done by Spearman correlation coefficients with confidence interval estimation by Fishers z-transformation, using the objective PA measures.
The index was further internally evaluated in the validation sample from the remaining sub-study population (n=911) by calculating the IPAI for each participant and using Spearman correlation coefficients as in the training sample.
A sensitivity analysis in participants who declared no current employment (n=699) was performed using Spearman correlations coefficients between the objective PA measures, the IPAI, the Cambridge Index and the Total Physical Activity Index.

Not all questions forming the IPAI were available from the EPIC baseline questionnaire (Appendix 1). Therefore, for baseline PA level calculation in the EPIC cohort, an alternative IPAI ($IPAI_{BASE}$) was calculated using only questions available in the EPIC baseline data set.

4.4.2 Measurement error correction methods

The full EPIC dataset was compared with the internal validation dataset by calculating the mean and standard deviation (SD) for potential covariates.
In the internal validation dataset of 1,339 participants the baseline $IPAI_{BASE}$ was calculated (5.2.2).

$IPAI_{BASE,}$ was $\log_2$ transformed and a randomly selected constant value of 11 was added, as the $IPAI_{BASE}$ values included negative numbers and ranged from -1.91 to 1.76.
Next, the $IPAI_{BASE}$ distribution at sub-study was compared with the $IPAI_{BASE}$ distribution at baseline.

The relationship between the $IPAI_{BASE}$ and the acceleration counts was analyzed using graphical methods. Different parametric and non-parametric approaches were used:

- Fractional polynomials regression with FP1= $logIPAI_{BASE}^{-2}$; $FP2_1$= $logIPAI_{BASE}^{3}$ and $FP2_2$ = $logIPAI_{BASE}^{3}$ * $log(logIPAI_{BASE})$
- Linear regression analysis
- Spline regression (degree=3, knots=3)
- Linear regression without outliers: according to Coock's D and the leverage values for outlier observations were deleted > 4/1399 Coock's D and >4/1339 leverage
- Segmented regression: according to Coock's D and the leverage values for outlier a break point was chosen: log$\mathbf{IPAI_{BASE}}$>3.58 and log$\mathbf{IPAI_{BASE}}$ <3.38 for grouping the participants in a low, a normal and a high outlier group (low <3.38; normal ≥3.38 <3.58; high ≥3.58)
- Linear regression with shifted outliers: According to Cooc'sD and the leverage values for outlier a cut-point was chosen: log$\mathbf{IPAI_{BASE}}$≥3.58 and log$\mathbf{IPAI_{BASE}}$ <3.38 and the over and underestimated values were shifted towards the mean ±0.1

After adding additional covariates (age, sex and BMI category) and stratifying by study center (Potsdam, Heidelberg) the $IPAI_{BASE}$ was again plotted against AC using similar approaches as in the unadjusted plots.

In order to determine whether the questionnaire PA outliers should be treated as under- or overestimations or might truly reflect activity, the lowest and highest log$\mathbf{IPAI_{BASE}}$ values were compared with the lowest and highest objective PA measures. Therefore, the mean and SD on information about h/week of sport, cycling and television viewing was calculated for log$\mathbf{IPAI_{BASE}}$ < percentile 5 and > percentile 95 and compared with AC < percentile 5 and > percentile 95 and PAEE kJ/kg/day < percentile 5 and > percentile 95.

Based on the graphic representation of the relationship between the objective measurement and the questionnaire derived PA scores the segmented regression model was chosen for baseline data calibration. Thereby, the results from the mean and SD information were taken into account.

The regression calibration coefficients were derived from the internal validation dataset. They were stratified by center, based on the underlying segmented regression calibration model and took into account covariates Z (age, sex and BMI category at time of testing) and fitted to the baseline data. Consequently, a continuous PA measure for the baseline data was created – **Questionnaire-based accelerometer counts ($\mathbf{Qb_{AC}}$)** [counts/min/day].

4.4.3 Physical activity and chronic diseases methods

The Cambridge Index at baseline was used as exposure in the first part of the analysis. Moreover, the calibrated PA data – Qb_{AC}, divided in quartiles was used for the second part in order to compare non-calibrated and calibrated risk estimates.

The proportional hazards assumption was tested by plotting Schoenfeld residuals (98). Disease risk was estimated by calculating hazard ratios (HR) and 95% CI unsing Cox proportional hazards regression. Age was the underlying time variable with the subject's age at recruitment as start-time and stop-time at the age of diagnosis or censoring, respectively. Three models for each outcome (overall chronic diseases, type 2 diabetes, MI, stroke, and cancer) were calculated based on the preceding DAG confounder selection (4.3):

Model 1: Raw model, without adjustment.

Model 2: Adjustment for the total effect estimation: sex, educational attainment, stratified by age

Model 3: Adjustment for the direct effect estimation (the model varies among the endpoints):

Overall chronic diseases: sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50 g/day, ≥50<100 g/day, ≥100<150 g/day ≥150 g/day), vegetable intake (<100 g/day, ≥100<200 g/day, ≥200<300 g/day ≥300 g/day), red meat intake (<30 g/day, ≥30<60 g/day, ≥60<90 g/day ≥90 g/day), alcohol intake (<5 g/day, ≥5<10 g/day, ≥10<15 g/day, ≥15<20 g/day ≥20 g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), vitamin use (yes/no), mineral use (yes, no), stratified by age.

Type 2 diabetes: sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50 g/day, ≥50<100 g/day, ≥100<150 g/day ≥150 g/day), vegetable intake (<100 g/day, ≥100<200 g/day, ≥200<300 g/day ≥300 g/day), red meat intake (<30 g/day, ≥30<60 g/day, ≥60<90 g/day ≥90 g/day), alcohol intake (<5 g/day, ≥5<10 g/day, ≥10<15 g/day, ≥15<20 g/day ≥20 g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), stratified by age.

Myocardial infarction: sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50 g/day, ≥50<100 g/day, ≥100<150 g/day ≥150 g/day), vegetable intake (<100 g/day, ≥100<200 g/day, ≥200<300 g/day ≥300 g/day), red meat intake (<30 g/day, ≥30<60 g/day, ≥60<90 g/day ≥90 g/day), alcohol intake (<5 g/day, ≥5<10 g/day, ≥10<15 g/day, ≥15<20 g/day ≥20 g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), stratified by age.

Stroke: sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50 g/day, ≥50<100 g/day, ≥100<150 g/day ≥150 g/day), vegetable intake (<100 g/day, ≥100<200

g/day, ≥200<300 g/day ≥300 g/day), red meat intake (<30 g/day, ≥30<60 g/day, ≥60<90 g/day ≥90 g/day), alcohol intake (<5 g/day, ≥5<10 g/day, ≥10<15 g/day, ≥15<20 g/day ≥20 g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), stratified by age.

Cancer: sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50 g/day, ≥50<100 g/day, ≥100<150 g/day ≥150 g/day), vegetable intake (<100 g/day, ≥100<200 g/day, ≥200<300 g/day ≥300 g/day), red meat intake (<30 g/day, ≥30<60 g/day, ≥60<90 g/day ≥90 g/day), alcohol intake (<5 g/day, ≥5<10 g/day, ≥10<15 g/day, ≥15<20 g/day ≥20 g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), vitamin use (yes/no), mineral use (yes, no), stratified by age.

In order to take into account that cancer is a disease of long latency and of high complexity, a sensitivity analysis was performed, excluding all cases that occurred up to 3 years after study enrollment (1,795 cancer cases). Moreover, two cancer types, that were shown in literature to be associated with PA were analyzed: breast cancer (187 cases) and colorectal cancer (106 cases); both with restriction to cases that occurred 3 years after study enrolment.

HRs were presented for non-calibrated and calibrated PA baseline data separately. Furthermore, center specific, calibrated HRs, for all analyzed disease endpoints were calculated and presented in the supplementary tables in Appendix 3.

All analyses were performed with SAS Enterprise Guide version 4.3.

5. Results: Development and evaluation of the Improved Physical Activity Index *

5.1 Descriptive statistics

For the development of the IPAI, the study population was spitted into a training and validation sample. Descriptive analyses showed no significant difference between the training and the validation sample (Table 3). The participants had a mean age of 65 years and spent 8.4 kJ/kg/day of PAEE. Of them, 49% were men, 52% were non-working, 32% performed sedentary work, 10% performed standing work, and the remaining 6% were engaged in manual or heavy manual work.

Table 3 Study population characteristics of the EPIC sub-study training (n=433) and validation (n=911) sample.

		Training sample n=433	Validation sample n=911
Sex (%women)		50.81	51.59
Age at recruitment (years)		63.53±8.55	65.74±7.99
Occupational activity (%)	Non-working	51.27	52.58
	Sedentary	32.33	31.28
	Standing	9.70	10.43
	Manual	6.24	4.39
	Heavy manual	0.46	1.32
Total Physical Activity Index (%)	Inactive	20.55	20.42
	Moderately inactive	31.18	35.78
	Moderately active	42.26	38.20
	Active	6.0	5.60
Cambridge index (%)	Inactive	8.08	9.33
	Moderately inactive	35.80	34.25
	Moderately active	28.41	28.10
	Active	27.71	28.32
Acceleration counts		30.47±17.26	29.09±13.9
PAEE (kJ/kg/day)		8.54±3.66	8.29±3.68
Sedentary time (min/day)		1070±135	1077±136
PAL		1.59±0.20	1.58±0.20

*In the framework of this thesis, parts of the results on the Improved Physical Activity Index have been published by the author in similar text: Wientzek A, Vigl M, Steindor K, Brühmann B, Bergmann MM, Harttig U, Katzke V, Kaaks R, Boeing H. The Improved Physical Activity Index for measuring physical activity in EPIC Germany. PLoS One. 2014 Mar 18;9(3).

5.2 Index development

5.2.1 The Improved Physical Activity Index

Based on the Spearman correlation coefficients between a set of RPAQ questions about the frequency of a particular sport and the objective measures AC, PAEE, and PAL variables that should be included into the IPAI, were selected. The following variables were positively correlated with r > 0.1: nordic walking, cycling, high impact aerobics, exercises with weights, floor exercises, dancing, jogging, inline skating, alpine skiing. Negatively correlated with at least two of the objectively measured PA variables were swimming, swimming-competitive, gardening, “do it yourself” activities, table tennis and horse-riding. Questions about the duration of these sports showed very similar correlations. Questions about the residency area from the ALPHA questionnaire showed expected correlation directions. Two questions (walking/cycling unsafe due to road traffic and due to high crime rate) were negatively correlated with the objectively measured PA. The remaining questions were positively correlated or showed no correlation.

The sport score, residency area, TV score and PC score were calculated as described in the method section.

The third step - Spearman correlation between the scores, the corresponding single variables and AC revealed that the sport score (r=0.33), PC weekend evening (r=0.12), and the TV score (r=-0.31) were the variables that correlated highest with AC.

Multiple linear regression with stepwise variable selection gave a set of five variables explaining most of the variance: TV score (partial R=0.086), sport score (partial R=0.06), type of work (partial R=0.02), cycling (h/week, partial R=0.01) and PC weekend evening (partial R=0.001). The model explained 18% of the variance in AC. For the chosen variables, univariate analyses were performed and the variable range was determined (Table 4). The residency area score did not enter the model.

Table 4 Mean, standard deviation (SD), minimum (min), maximum (Max) and range values of variables used in the Improved Physical Activity Index (IPAI) derived from 433 participants of the EPIC Germany sub-study

	Mean	SD	Min	Max	Range
Sport score	7.44	5.68	0	30	30
cycle	2.26	3.19	0	20	20
Type of work	0.72	0.91	0	4	4
TV score	5.58	1.7	1.3	12	11
PC weekend evening	1.87	0.96	1	6	5

The variables were standardized by their range to account for the differences in the ranges of the absolute variable values and to assign each variable an equal weight in the index. Finally, for every participant, the index items were summed up according to their direction they were correlated with AC:

$$\boldsymbol{IPAI} = (type\ of\ work/\mathbf{4}) + (cycling\ /\mathbf{20}) + (sport\ score/\mathbf{30}) - (TV\ score/\mathbf{11}) + (PC\ weekend\ evening/\mathbf{5}) \quad [1.8]$$

In order to classify the subjects into a particular activity level IPAI score values were ascribed to 5 IPAI activity levels: inactive, moderately inactive, moderately active, active and very active as described in the methods section (Chapter 4.5.1).

5.2.2 The Baseline Improved Physical Activity Index

To facilitate IPAI calculation from EPIC baseline data an alternative index was set up. Therefore, available data from the baseline PA questionnaire was used and PA dimensions similar to the IPAI were derived. This included type of work (sedentary, standing, manual, hard), cycling (h/week, average from summer and winter), sport (h/week average from summer and winter), TV viewing (h/week). As PC use was not asked in the baseline PA questionnaire, it could not be included in the baseline IPAI ($IPAI_{BASE}$). Using the same index building rules, the $IPAI_{BASE}$ was developed.

$$\boldsymbol{IPAI_{BASE}} = (type\ of\ work/\mathbf{4}) + (cycling\ /\mathbf{14.50}) + (sports\ /\mathbf{11.25}) - (watching\ TV/\mathbf{7}) \quad [1.9]$$

5.3 Validity and evaluation of the new indexes

5.3.1 The IPAI and the $IPAI_{BASE}$

The validity of the index was tested and compared with calculated values of existing indices (Cambridge Index and Total Physical Activity Index, Table 5). The IPAI showed moderate validity used continuously as well as categorical with r≥0.4 for AC and PAEE and r>0.3 for MVPA and PAL. The established indices showed smaller correlation coefficients with objective measures of PA.

Table 5 Spearman correlation coefficients and 95% confidence intervals (95%CI) between accelerometer counts (AC), physical activity energy expenditure (PAEE), physical activity level (PAL), moderate and vigorous physical activity (MVPA), sedentary time and the Improved Physical Activity Index (IPAI) (continuous and categorical), the Cambridge Index and the Total Physical Activity Index in 433 participants of the EPIC Germany study training sample.

Spearman Correlation Coefficients, N = 433		IPAI	IPAI categorical	Cambridge Index	Total PA Index
AC (counts/min)	r	0.43	0.44	0.31	-0.01
	95%CI	0.35,0.50	0.36,0.51	0.22,0.39	-0.11,0.08
PAEE (kJ/kg/day)	r	0.40	0.40	0.32	-0.05
	95%CI	0.32,0.48	0.32,0.48	0.23,0.40	-0.15,0.04
PAL categories	r	0.32	0.32	0.25	0.01
	95%CI	0.25,0.42	0.25,0.41	0.16,0.33	-0.08,0.10
MVPA (h/day)	r	0.34	0.34	0.25	0.04
	95%CI	0.24,0.40	0.24,0.41	0.15,0.33	-0.05,0.14
sedentary time (h/day)	r	-0.28	-0.27	-0.22	-0.00
	95%CI	-0.36,-0.19	-0.36,-0.18	-0.31,-0.12	-0.10,0.09

Table 6 Spearman correlation coefficients and 95% confidence intervals (95%CI) between accelerometer counts (AC), physical activity energy expenditure (PAEE), physical activity level (PAL), moderate and vigorous physical activity (MVPA), sedentary time and the Improved Physical Activity index (IPAI) (continuous and categorical) the Cambridge Index and the Total Physical Activity Index in 911 participants of the EPIC Germany study validation sample.

Spearman Correlation Coefficients, N=911		IPAI	IPAI categorical	Cambridge Index	Total PA Index
AC (counts/min)	r	0.40	0.39	0.32	-0.04
	95%CI	0.35,0.46	0.33,0.44	0.26,0.38	-0.10,0.03
PAEE (kJ/kg/day)	r	0.33	0.32	0.31	0.02
	95%CI	0.28,0.39	0.26,0.38	0.25,0.37	-0.04,0.09
PAL categories	r	0.30	0.29	0.25	0.05
	95%CI	0.24,0.36	0.22,0.34	0.19,0.31	-0,01,0.12
MVPA (h/day)	r	0.28	0.26	0.22	0.05
	95%CI	0.22,0.34	0.20,0.32	0.16,0.28	-0.02,0.11
sedentary time (h/day)	r	-0.27	-0.26	-0.26	-0.06
	95%CI	-0.33,-0.21	-0.32,-0.20	-0.32,-0.20	-0.13,0.00

In the validation sample of 911 participants, the IPAI was calculated and the results were again compared with existing indices (Table 6). The correlation coefficients were lower compared to those from the training sample. The correlations between the IPAI and AC were still higher than the correlations between the established indices and AC. For other objectively measured PA measures the correlation coefficients were similar for the IPAI and the Cambridge Index. No significant correlations with the objective measures of PA could be found for the Total Physical Activity Index.

Finally, the performance of the $IPAI_{BASE}$ was evaluated (Table 7). The correlation coefficients were smaller than for the IPAI but still between r=0.30 and r=0.39. The categorical $IPAI_{BASE}$ also showed moderate correlation coefficients with objectively measured PA.

Table 7 Spearman correlation coefficients and 95% confidence intervals (95%CI) between accelerometer counts (AC), physical activity energy expenditure (PAEE), physical activity level (PAL), moderate and vigorous physical activity (MVPA), sedentary time and the Baseline Improved Physical Activity index ($IPAI_{BASE}$) (continuous and categorical) Index in 1,344 participants of the EPIC Germany study

Spearman Correlation Coefficients N=1,344			
		$IPAI_{BASE}$	$IPAI_{BASE}$ categorical
AC (counts/min)	**r**	0.39	0.38
	95%CI	0.34;0.43	0.33;0.42
PAEE (kJ/kg/day)	**r**	0.34	0.33
	95%CI	0.29;0.39	0.28;0.37
PAL categories	**r**	0.31	0.29
	95%CI	0.26;0.35	0.24;0.34
MVPA (h/day)	**r**	0.30	0.28
	95%CI	0.25;0.34	0.23;0.33
sedentary time (h/day)	**r**	-0.27	-0.25
	95%CI	-0.32;-0.22	-0.30;-0.20

5.3.2 Sensitivity analysis

The Spearman correlation results for the sensitivity analysis in non-working participants are presented in Table 8. The coefficients for the IPAI as well as for the Cambridge Index tended to be lower in unemployed compared to employed participants. The coefficients between the Total Physical Activity Index and objectively measured PA increased and reached statistical significance. However, there was still a moderate correlation between the objective PA measures and the IPAI. The correlation between the IPAI and the PA measures was significantly higher than for the established indices.

Table 8 Spearman correlation coefficients and 95% confidence intervals (95%CI) between accelerometer counts (AC), physical activity energy expenditure (PAEE), physical activity level (PAL), moderate and vigorous physical activity (MVPA), sedentary time and the Improved Physical Activity index (IPAI) (continuous and categorical) the Cambridge Index and the Total Physical Activity Index in 699 non-working participants of the EPIC Germany sub-study.

Spearman Correlation Coefficients, N = 699					
		IPAI	IPAI categories	Cambridge Index	Total PA Index
AC (counts/min)	**r**	0.34	0.33	0.18	0.08
	95%CI	0.28,0.41	0.27,0.40	0.11,0.25	0.01,0.16
PAEE (kJ/kg/day)	**r**	0.29	0.27	0.15	0.10
	95%CI	0.22,0.36	0.20,0.34	0.08,0.22	0.03,0.18
MVPA (h/day)	**r**	0.28	0.26	0.18	0.11
	95%CI	0.20,0.34	0.19,0.33	0.11,0.25	0.03,0.18
PAL categories	**r**	0.27	0.25	0.14	0.11
	95%CI	0.20,0.34	0.18,0.32	0.07,0.22	0.04,0.18
sedentary time (h/day)	**r**	-0.24	-0.22	-0.11	-0.09
	95%CI	-0,30.-,016	-0,29,-0.15	-0,18,-0.04	-0.17,-0.02

6. Results: Baseline data calibration and the associations between physical activity and chronic disease risk

6.1 Descriptive statistics

The EPIC baseline study participants were compared with the sub-study participants in Table 9. In the overall cohort, 6% more women took part than in the sub-study. The age at recruitment, educational attainment, smoking status, PA levels as well as, dietary variables were similar in both groups.

Table 9 Study population characteristics of the European Prospective Investigation into Cancer and Nutrition (EPIC) Germany study of 45,855 participants and the 1,339 sub-study participants.

		EPIC-Germany (n=45855)	EPIC sub-study (n=1399)
Sex (% women)		58.4	52.5
Age at recruitment (years)		50.0 ± 8.5	50.1 ± 8.0
Educational attainment (%)	Primary school completed	22.3	18.0
	Technical/ professional school	36.0	34.6
	Secondary school	7.0	7.7
	Higher education	34.3	39.6
Smoking status (%)	Non smoker	46.3	45.6
	Former smoker	32.3	35.7
	Current smoker	21.2	18.4
Cambridge index (%)	Inactive	16.1	13.1
	Moderately inactive	36.6	37.6
	Moderately active	26.5	28.7
	Active	20.7	20.7
Cycling and sports (h/week)		3.4 ± 3.8	3.6 ± 3.8
Red meat intake (g/day)		30.2 ± 26.2	30.6 ± 26.5
Fruit intake (g/day)		138.9 ± 100.2	137.2 ± 98.4
Vegetable intake (g/day)		123.7 ± 61.0	123.3 ± 58.6

6.2 Baseline physical activity data calibration

The $IPAI_{BASE}$ distribution in percentiles (Pct) at sub-study was compared with the $IPAI_{BASE}$ distribution at baseline (Table 10). The comparison showed a very similar distribution.

Table 10 Improved Physical Activity Index (IPAI) baseline values distribution in the EPIC baseline assessment in 45,855 participants between 1994 and 1998 and in the sub-study assessment in 1,399 participants between 2010 and 2012

	Pct5	Pct10	Pct25	Pct50	Pct75	Pct90	Pct95
Baseline $IPAI_{BASE}$	3.44	3.45	3.48	3.50	3.53	3.57	3.59
Sub-study $IPAI_{BASE}$	3.39	3.41	3.44	3.48	3.52	3.56	3.58

Next the relationship between the $IPAI_{BASE}$ and the AC was determined by different regression approaches (see chapter 4.4.2) and presented graphically in Figure 10.

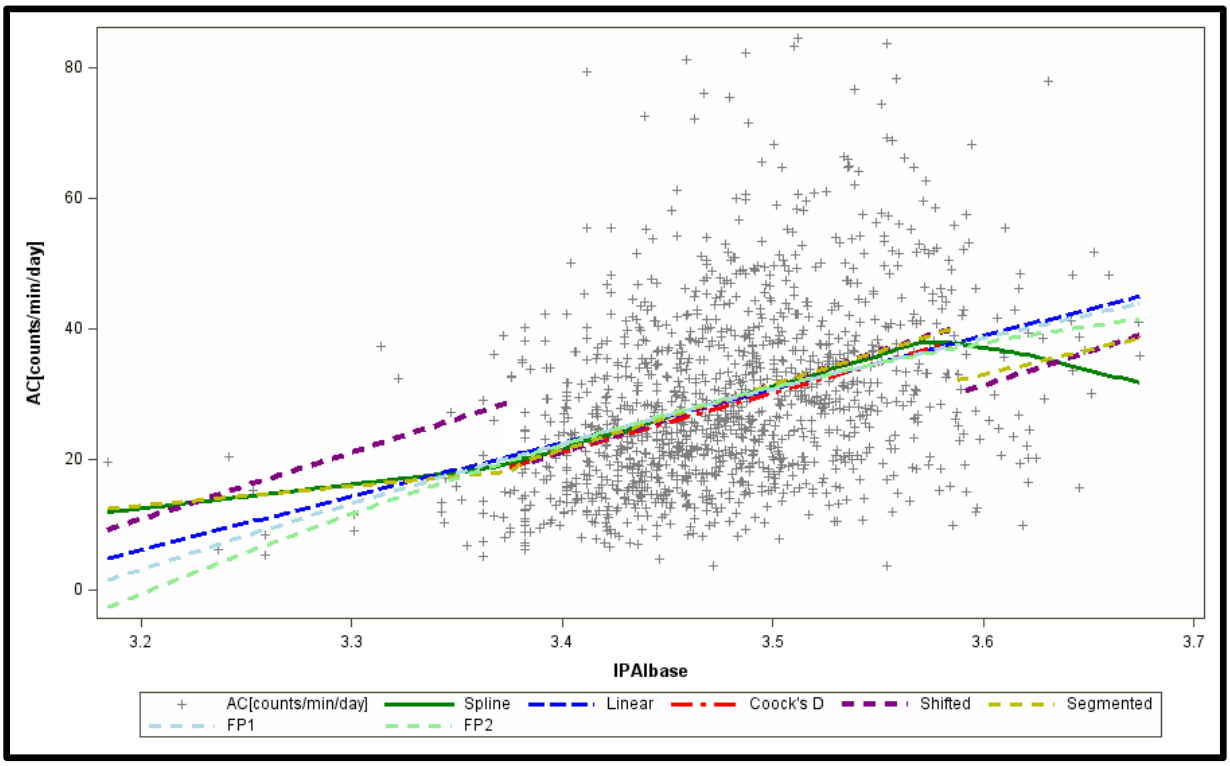


Figure 10 Plot between accelerometer counts (AC) and the baseline Improved Physical Activity Index ($IPAI_{BASE}$) values using different approaches.

Age, sex and BMI category were added to the model and stratified by center, and the plots were drawn using the same approaches as in the unadjusted analysis (Figure 11).

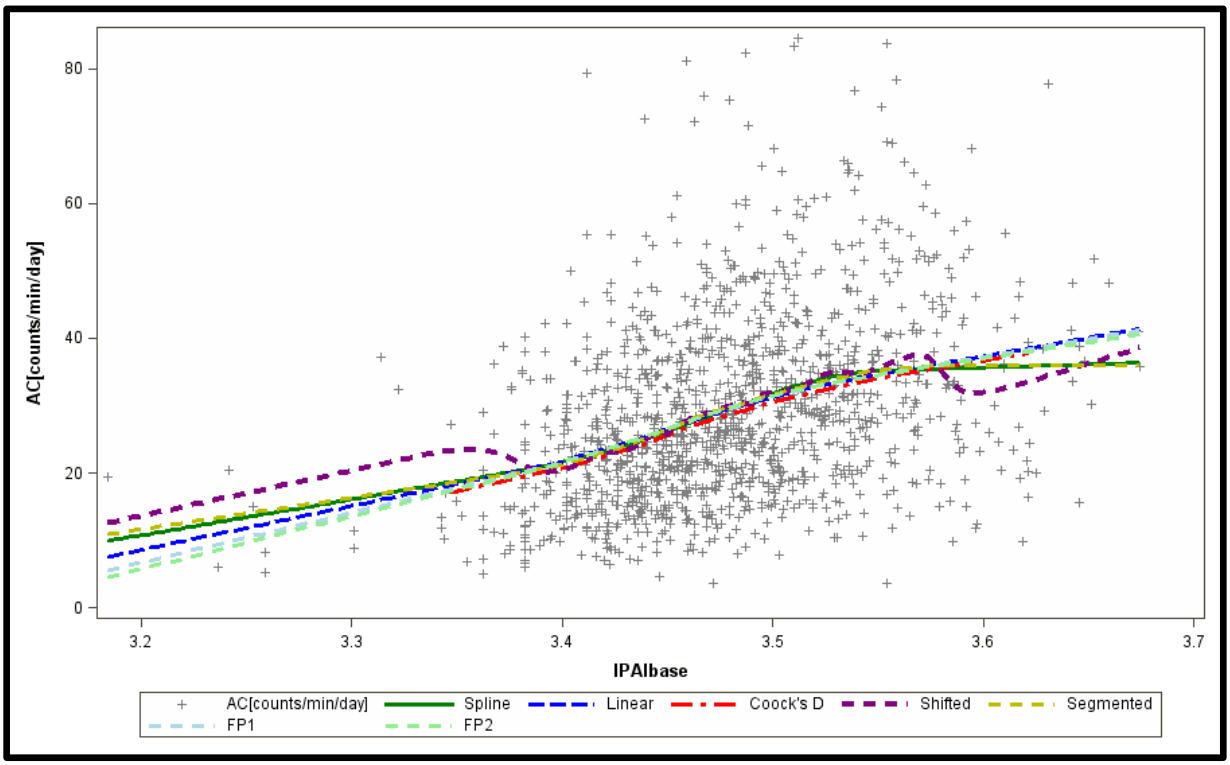


Figure 11 Plot between accelerometer counts (AC) and the baseline Improved Physical Activity Index ($IPAI_{BASE}$), adjusted for age, sex and Body Mass Index (BMI), using different approaches.

The differences in cycling between the highest $IPAI_{BASE}$ and the highest PAEE or AC category were 4.33 h/week and 4.81 h/week, respectively (Table 11). Similar were the differences for sport activity. The participants with the highest questionnaire derived PA level reported to spend 3.23 h/week (AC) and 3.8 h/week (PAEE) more in sports than the participants in the highest objectively measured PA level; the participants with the lowest $IPAI_{BASE}$ level reported 5.66h/day of TV viewing which was 1.8 h/day (AC) and 2.29 h/day (PAEE) more than the objectively measured PA.

Table 11 Mean and standard deviation (SD) of cycling (h/week), sport (h/week) and television viewing (TV) in the highest and lowest percentiles of the Improved Physical Activity Index (IPAI), the objectively measured physical activity by acceleration counts (AC, counts/min) and physical activity energy expenditure (PAEE, kJ/kg/day)

	$IPAI_{BASE}$ Pct95>	$IPAI_{BASE}$ <Pct5	AC >Pct95	AC <Pct5	PAEE >Pct95 kJ/kg/day	PAEE <Pct5 kcal/day
n=	66	67	66	65	66	68
Cycle	7.32±4.73	0.44±1.30	2.99±3.16	1.49±2.47	2.51±3.36	1.91±3.05
Sporty	6.19±4.36	0.29±0.53	2.96±2.69	1.54±2.33	2.39±2.79	1.05±1.53
TV viewing	1.88±1.24	5.66±2.29	2.05±1.32	3.86±2.26	2.34±1.16	3.37±1.77

After graphical model fit comparison and the quantitative data distribution analysis it was decided that the calibration method should include all participants, take into account the questionnaire over- and underestimation of PA and allow cut-point modulation by Coock's D. Therefore, baseline PA data were calibrated by fitting the segmented regression coefficients to the baseline data and thereby creating Qb_{AC}. This step was performed automatically through the software, nevertheless, the regression model coefficients for each center and Coock's D strata (the low stratum was estimated jointly for Potsdam and Heidelberg to increase power) can be found below:

Heidelberg:

High ($IPAI_{BASE}$≥3.58): $36.5 \cdot log_2(IPAI_{BASE}) - 10.61 \cdot sex - 0.21 \cdot age - 2.62 \cdot BMI\ category$ [2.0]

Norm ($IPAI_{BASE}$ ≥3.38 <3.58): $73.41 \cdot log_2(IPAI_{BASE}) - 1.29 \cdot sex - 0.30 \cdot age - 3.48 \cdot BMI\ category$ [2.1]

Potsdam:

High ($IPAI_{BASE}$≥3.58): $16.95 \cdot log_2(IPAI_{BASE}) - 0.54 \cdot sex - 0.70 \cdot age - 3.85 \cdot BMI\ category$ [2.2]

Norm ($IPAI_{BASE}$ ≥3.38 <3.58): $73.64 \cdot log_2(IPAI_{BASE}) + 0.07 \cdot sex - 0.37 \cdot age - 2.47 \cdot BMI$ category [2.3]

Potsdam and Heidelberg:

Low ($IPAI_{BASE}$<3.38): $36.22 \cdot log_2(IPAI_{BASE}) - 1.36 \cdot sex - 0.33 \cdot age - 0.93 \cdot BMI\ category$ [2.4]

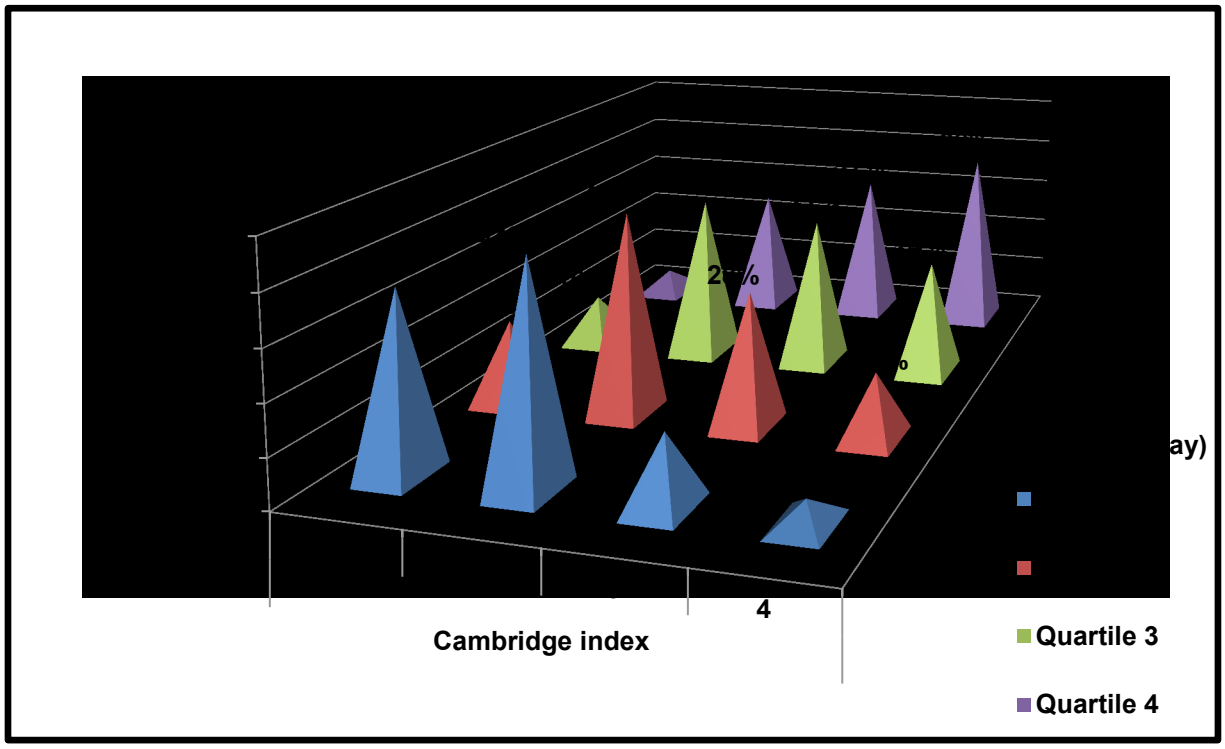


Figure 12 Cross-tabulation between the Cambridge Index and the calibrated acceleration counts in the European Prospective Investigation into Cancer and Nutrition Germany sub-study of 1,339 participants.

The Cambridge Index and the $Qb_{AC,}$ devided in quartiles, were cross-tabulated and are shown in Figure 12. The overall trend showed that the higher the Cambridge Index the higher the Qb_{AC} quartile, but there are some observations that where shifted towards a higher or a lower PA level. 5% of the observations that were former classified as active changed towards the lowest Qb_{AC} quartile and vice versa, 5% changed from the inactive level towards the highest Qb_{AC} quartile. The Pearson correlation between the Qb_{AC} and the Cambridge index was r=0.46 (0.45;0.46), between the Qb_{AC} and the objectively measured AC r=0.35 (0.30;0.40) and between the Cambridge Index and the objectively measured AC r=0.16 (0.13;0.24).

The means of AC and Qb_{AC} differed by 6.7 counts/min/day (AC=29.5 counts/min/day (SD=15.1) and Qb_{AC} =36.2 counts/min/day (SD=6.2)).

6.3 Physical activity and the risk of chronic diseases

6.3.1 Physical activity and risk of overall chronic diseases

At first, Schoenfeld residuals were plotted against age at first event to assess the proportional hazards assumption (an example is shown in Figure 13).

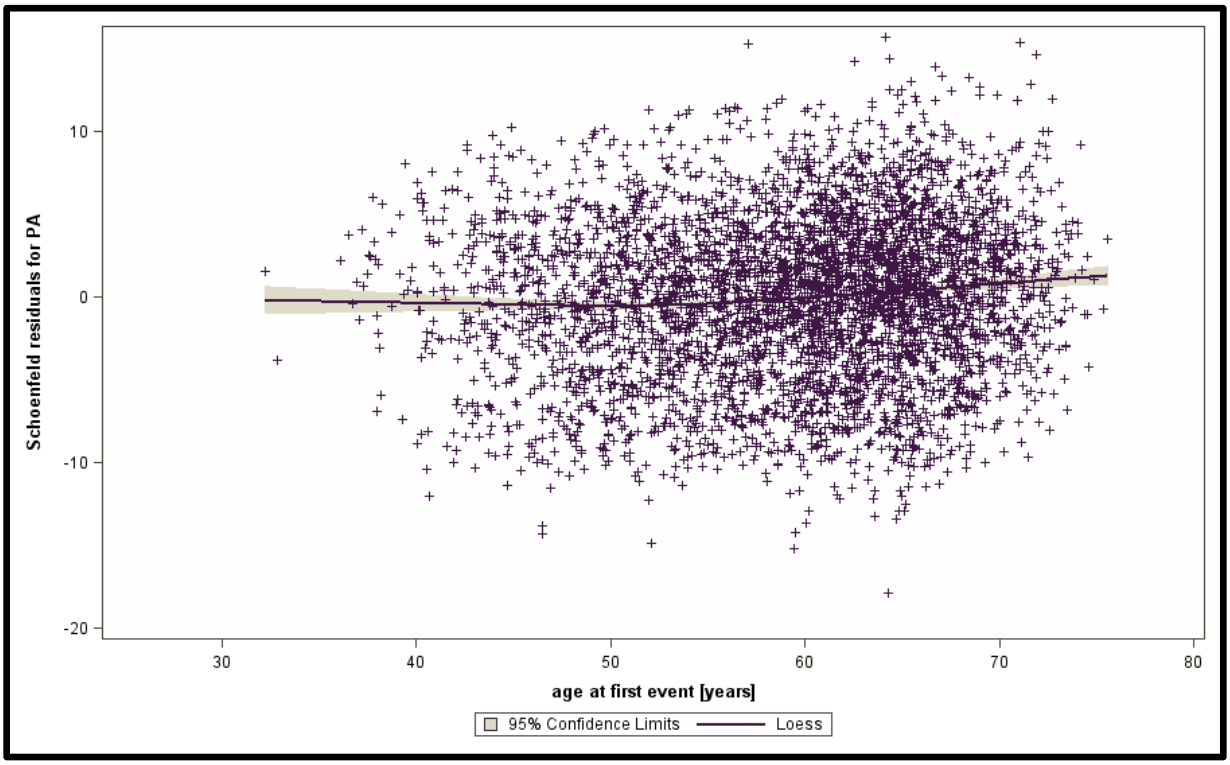


Figure 13 Schoenfeld residuals plot for physical activity (PA) and age at first event (years) for the proportional hazards assumption test

Next, the associations between PA and the risk of overall chronic diseases were evaluated with Cox proportional hazards regression for non-calibrated and calibrated PA data (Table 12). The risk estimates were lower for the calibrated compared to the non-calibrated PA data. The differences between the calibrated and non-calibrated estimates varied between quartiles from 11% to 32%.

The lowest risk was found for the highest PA quartile in model 2 with the calibrated data, indicating a 60% risk reduction for overall chronic diseases. In the second quartile a risk reduction of 33% was observed. Risk estimates derived from model 1 were higher indicating negative confounding by sex and educational attainment. Center specific risk estimates showed no differences between Potsdam and Heidelberg (Supplementary table 1).

Figure 14 shows the inverse relationship between calibrated PA - Qb_{AC} and the risk of chronic disease development, for each individual of the EPIC-Germany study.

Table 12 Associations between non-calibrated (Cambridge Index) and calibrated (Qb_{AC}) physical activity (PA) measures and the risk of overall chronic diseases in EPIC-Germany (n=45,855).

Overall chronic diseases (cases n=4,508)					
Non-calibrated - Cambridge index					
	Inactive	Moderately inactive	Moderately active	Active	p-trend
Cases n=	986	1631	1084	807	
Model 1	1	0.81(0.75;0.88)	0.79(0.72;0.86)	0.78(0.71;0.85)	<.0001
Model 2	1	0.81(0.75;0.87)	0.76(0.70;0.83)	0.72(0.66;0.80)	<.0001
Model 3	1	0.85(0.79;0.92)	0.84(0.77;0.91)	0.81(0.74;0.90)	<.0001
Calibrated - Qb_{AC} [counts/min/day]					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend
Cases n=	2067	1262	763	416	
Model 1	1	0.70(0.65;0.76)	0.54(0.49;0.59)	0.42(0.37;0.47)	<.0001
Model 2	1	0.67(0.63;0.73)	0.51(0.47;0.56)	0.40(0.35;0.46)	<0.001
Model 3	1	0.82(0.76;0.89)	0.72(0.65;0.80)	0.67(0.57;0.78)	<0.001

Model 1 – not adjusted
Model 2 – adjusted for sex and educational attainment (none, primary school completed, technical/professional school, secondary school, longer education) stratified by age
Model 3 – adjusted for sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50g/day, ≥50<100g/day, ≥100<150g/day ≥150g/day), vegetable intake (<100g/day, ≥100<200g/day, ≥200<300g/day ≥300g/day), red meat intake (<30g/day, ≥30<60g/day, ≥60<90g/day ≥90g/day), alcohol intake (<5g/day, ≥5<10g/day, ≥10<15g/day, ≥15<20g/day ≥20g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), vitamin use (yes/no), mineral use (yes, no), stratified by age

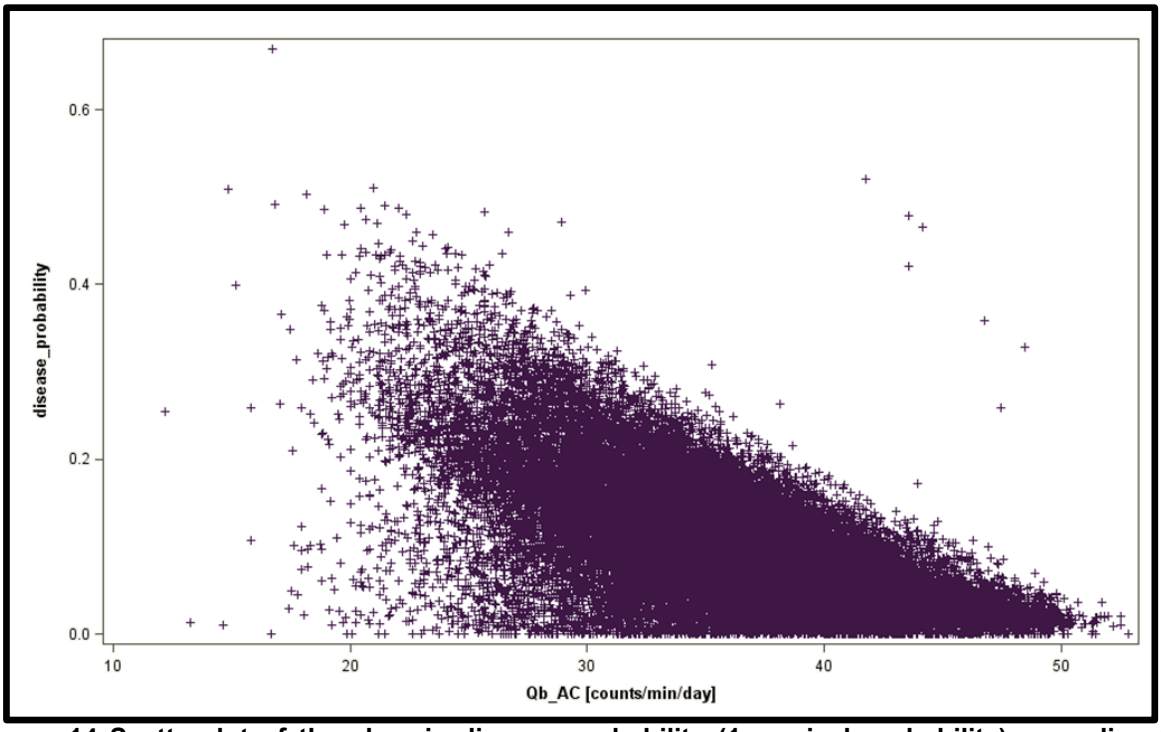


Figure 14 Scatterplot of the chronic disease probability (1-survival probability) according to physical activity measured by questionnaire-based accelerometer counts (Qb_{AC}) in 45,855 participants of EPIC Germany.

6.3.2 Physical activity and risk of type 2 diabetes

The associations between PA and the risk of type 2 diabetes are presented in Table 13. The risk estimates were lower for the calibrated compared to the non-calibrated PA data. The difference between the calibrated and non-calibrated estimates varied between quartiles and amounted from 7% to 57%.

The lowest risk was found for the highest PA quartile in model 2 with non-calibrated data (HR=0.08). In all models from the second to fourth quartile there was an inverse association with type 2 diabetes risk. The trend analysis, showed an inverse linear relationship.

Center specific risk estimates showed no differences between Potsdam and Heidelberg (Supplementary table 2).

Table 13 Associations between non-calibrated (Cambridge Index) and calibrated (Qb_{AC}) physical activity (PA) measures and the risk of type 2 diabetes in EPIC-Germany (n=45,855).

Type 2 diabetes (cases n=1,605) Non-calibrated - Cambridge index					
	Inactive	Moderately inactive	Moderately active	Active	p-trend
Cases n=	377	589	376	263	
Model 1	1	0.76(0.67;0.86)	0.70(0.60;0.80)	0.65(0.55;0.76)	<.0001
Model 2	1	0.75(0.66;0.86)	0.66(0.57;0.76)	0.57(0.48;0.67)	<.0001
Model 3	1	0.82(0.72;0.94)	0.77(0.67;0.89)	0.70(0.60;0.82)	<.0001

	Calibrated - Qb_{AC} [counts/min/day]				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend
Cases n=	955	423	167	60	
Model 1	1	0.42(0.37;0.47)	0.18(0.15;0.21)	0.08(0.06;0.11)	<.0001
Model 2	1	0.40(0.36;0.45)	0.16(0.14;0.20)	0.08(0.06;0.10)	<.0001
Model 3	1	0.75(0.66;0.86)	0.47(0.38;0.58)	0.40(0.29;0.55)	<.0001

Model 1 – not adjusted
Model 2 – adjusted for sex and educational attainment (none, primary school completed, technical/professional school, secondary school, longer education) stratified by age
Model 3 – adjusted for sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50g/day, ≥50<100g/day, ≥100<150g/day ≥150g/day), vegetable intake (<100g/day, ≥100<200g/day, ≥200<300g/day ≥300g/day), red meat intake (<30g/day, ≥30<60g/day, ≥60<90g/day ≥90g/day), alcohol intake (<5g/day, ≥5<10g/day, ≥10<15g/day, ≥15<20g/day ≥20g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), stratified by age.

6.3.3 Physical activity and risk of myocardial infarction

The associations between PA and the risk of CHD are presented in Table 14. Again, the risk estimates were lower for the calibrated compared to the non-calibrated PA data. The differences between the calibrated and non-calibrated estimates varied between quartiles from 2% to 34%.

Regarding the calibrated results, in model 2 a 60% risk reduction was present in the most active group for CHD. The lower risk in model 1among the most active participants indicated positive confounding by sex and educational attainment. In the highest quartile of model 3 a 35% risk reduction could be found, independently of mediators. The association showed a linear trend across PA quartiles in model 1 and 2 but not in model 3.

Center specific risk estimates demonstrated that the combined risk estimates were mainly driven by cases from Heidelberg (Supplementary table 3). In the highest compared to the lowest PA quartile a risk reduction of 73% was observed (model 2) and a 61% risk reduction independently of mediators (model 3). For Potsdam the risk estimates were less precise.

Table 14 Associations between non-calibrated (Cambridge Index) and calibrated (Qb_{AC}) physical activity (PA) measures and the risk of myocardial infarction in EPIC-Germany (n=45,855).

Myocardial Infarction (cases n=371)					
Non-calibrated - Cambridge index					
	Inactive	Moderately inactive	Moderately active	Active	p-trend
Cases n=	80	133	99	59	
Model 1	1	0.83(0.63;1.10)	0.91(0.67;1.22)	0.72(0.51;1.01)	0.127
Model 2	1	0.82(0.62;1.09)	0.84(0.63;1.14)	0.62(0.44;0.88)	0.015
Model 3	1	0.92(0.69;1.22)	0.99(0.73;1.33)	0.76(0.54;1.07)	0.206
Calibrated – Qb_{AC} [counts/min/day]					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend
Cases n=	152	117	81	21	
Model 1	1	0.92(0.72;1.19)	0.86(0.63;1.16)	0.38(0.23;0.62)	0.002
Model 2	1	0.87(0.67;1.12)	0.82(0.61;1.11)	0.40(0.24;0.67)	0.002
Model 3	1	1.05(0.80;1.39)	1.13(0.80;1.61)	0.65(0.37;1.16)	0.651

Model 1 – not adjusted
Model 2 – adjusted for sex and educational attainment (none, primary school completed, technical/professional school, secondary school, longer education) stratified by age
Model 3 – adjusted for sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50g/day, ≥50<100g/day, ≥100<150g/day ≥150g/day), vegetable intake (<100g/day, ≥100<200g/day, ≥200<300g/day ≥300g/day), red meat intake (<30g/day, ≥30<60g/day, ≥60<90g/day ≥90g/day), alcohol intake (<5g/day, ≥5<10g/day, ≥10<15g/day, ≥15<20g/day ≥20g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), stratified by age

6.3.4 Physical activity and risk of stroke

Table 15 demonstrates the associations between PA and the risk of stroke. In the non-calibrated dataset, a significant risk reduction was only found in the moderately active group, indicating a non-linear relationship.

When considering the calibrated data, the highest RR was found in Quartile 4, indicating a 46% risk reduction in model 2. The calibrated estimates, especially in model 1 and 2 showed a linear effect of PA on the risk of stroke.

The center specific estimates were linear but similar to the MI risk estimates, mainly driven by data from Heidelberg. In the highest quartile compared to the lowest, a risk reduction of 53% in model 2 and 55% in model 3 was shown. The risk estimates for Potsdam showed large confidence intervals (Supplementary table 4).

Table 15 Associations between non-calibrated (Cambridge Index) and calibrated (Qb_{AC}) physical activity (PA) measures and the risk of stroke EPIC-Germany (n=45,855).

Stroke (cases n=342)					
Non-calibrated - Cambridge index					
	Inactive	Moderately inactive	Moderately active	Active	p-trend
Cases n=	78	123	69	72	
Model 1	1	0.79(0.60;1.05)	0.65(0.47;0.91)	0.91(0.66;1.26)	0.374
Model 2	1	0.80(0.60;1.06)	0.64(0.46;0.89)	0.86(0.62;1.19)	0.197
Model 3	1	0.85(0.64;1.14)	0.72(0.52;1.01)	0.99(0.71;1.37)	0.701
Calibrated – Qb_{AC} [counts/min/day]					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend
Cases n=	131	110	73	28	
Model 1	1	1.10(0.82;1.40)	0.96(0.70;1.32)	0.50(0.31;0.81)	0.043
Model 2	1	1.06(0.81;1.39)	0.98(0.71;1.35)	0.54(0.33;0.87)	0.083
Model 3	1	1.13(0.85;1.52)	1.07(0.73;1.56)	0.59(0.33;1.06)	0.351

Model 1 – not adjusted
Model 2 – adjusted for sex and educational attainment (none, primary school completed, technical/professional school, secondary school, longer education) stratified by age
Model 3 – adjusted for sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50g/day, ≥50<100g/day, ≥100<150g/day ≥150g/day), vegetable intake (<100g/day, ≥100<200g/day, ≥200<300g/day ≥300g/day), red meat intake (<30g/day, ≥30<60g/day, ≥60<90g/day ≥90g/day), alcohol intake (<5g/day, ≥5<10g/day, ≥10<15g/day, ≥15<20g/day ≥20g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), stratified by age

6.3.5 Physical activity and risk of cancer

The associations between PA and the risk of cancer are presented in Table 16. In non-calibrated data a 10% - 14% lower risk of cancer was observed in all PA categories. The calibrated estimates showed no relationships between PA and overall cancer risk. There were no linear trends, neither in the non-calibrated nor in the calibrated estimates.

Center specific risk estimated showed no differences between Potsdam and Heidelberg (Supplementary table 5).

Table 16 Associations between non-calibrated (Cambridge Index) and calibrated (Qb_{AC}) physical activity (PA) measures and the risk of overall cancer in EPIC-Germany (n=45,855).

Overall cancer (cases n=2,190)					
Non-calibrated - Cambridge index					
	Inactive	Moderately inactive	Moderately active	Active	p-trend
Cases n=	451	786	540	413	
Model 1	1	0.88(0.78;0.98)	0.86(0.78;1.00)	0.90(0.79;1.03)	0.199
Model 2	1	0.87(0.78;0.98)	0.88(0.77;0.99)	0.89(0.78;1.02)	0.136
Model 3	1	0.88(0.77;0.99)	0.89(0.78;1.01)	0.90(0.79;1.03)	0.210
Calibrated – Qb_{AC} [counts/min/day]					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend
Cases n=	829	612	442	307	
Model 1	1	0.98(0.88;1.10)	1.04(0.91;1.18)	1.13(0.96;1.33)	0.197
Model 2	1	0.97(0.87;1.09)	1.03(0.90;1.17)	1.10(0.93;1.31)	0.316
Model 3	1	0.94(0.83;1.05)	0.97(0.83;1.13)	0.99(0.81;1.22)	0.882

Model 1 – not adjusted
Model 2 – adjusted for sex and educational attainment (none, primary school completed, technical/professional school, secondary school, longer education) stratified by age
Model 3 – adjusted for sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50g/day, ≥50<100g/day, ≥100<150g/day ≥150g/day), vegetable intake (<100g/day, ≥100<200g/day, ≥200<300g/day ≥300g/day), red meat intake (<30g/day, ≥30<60g/day, ≥60<90g/day ≥90g/day), alcohol intake (<5g/day, ≥5<10g/day, ≥10<15g/day, ≥15<20g/day ≥20g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), vitamin use (yes/no), mineral use (yes, no), stratified by age

The sensitivity analysis with restriction to cases that occurred after 3 years of study enrolment showed a persisting preventive effect of PA on overall cancer risk for the non-calibrated PA data (Table 17). The calibrated estimates in the crude model showed a linear risk increase for overall cancer with PA. However, results from model 2 and 3 indicate that it was due to confounding, and on the contrary risk tended to be slightly decreased in the second and third quartile.

Table 17 Associations between physical activity and risk of overall cancer. Sensitivity analysis with restriction to cases, that occurred after 3 years of study enrollment. EPIC-Germany (n=45,855)

Overall cancer (cases n=1,795)					
Non-calibrated - Cambridge index					
	Inactive	Moderately inactive	Moderately active	Active	p-trend
Cases n=	377	638	432	348	
Model 1	1	0.88(0.77;1.00)	0.89(0.78;1.02)	0.96(0.83;1.11)	0.729
Model 2	1	0.85(0.75;0.96)	0.84(0.73;0.96)	0.89(0.77;1.03)	0.172
Model 3	1	0.86(0.76;0.98)	0.85(0.74;0.98)	0.91(0.78;1.06)	0.277
Calibrated – Qb_{AC} [counts/min/day]					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend
Cases n=	698	504	341	252	
Model 1	1	1.06(0.95;1.20)	1.13(0.98;1.31)	1.47(1.23;1.75)	0.0002
Model 2	1	0.93(0.82;1.05)	0.91(0.78;1.05)	1.03(0.86;1.24)	0.691
Model 3	1	0.91(0.79;1.03)	0.88(0.74;1.04)	0.96(0.77;1.21)	0.398

Model 1 – not adjusted
Model 2 – adjusted for sex and educational attainment (none, primary school completed, technical/professional school, secondary school, longer education) stratified by age
Model 3 – adjusted for sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50g/day, ≥50<100g/day, ≥100<150g/day ≥150g/day), vegetable intake (<100g/day, ≥100<200g/day, ≥200<300g/day ≥300g/day), red meat intake (<30g/day, ≥30<60g/day, ≥60<90g/day ≥90g/day), alcohol intake (<5g/day, ≥5<10g/day, ≥10<15g/day, ≥15<20g/day ≥20g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), vitamin use (yes/no), mineral use (yes, no), stratified by age

The second sensitivity analysis included two most important cancer types: breast cancer and colorectal cancer. Both were analyzed with restriction to cases that occurred after at least years of study enrollment. The results are presented in Table 18 and Table 19.

The non-calibrated results showed a strong inverse relationship for PA and breast cancer (risk reduction: 39% to 50% in model 2). The respective figure for colorectal cancer was similar (risk reduction: 27% to 74% in model 2). The relationships were linear in both cancer types.

The calibrated results showed a somehow different pattern. For breast cancer in the second and third quartile no relationship could be found. In the fourth quartile, after adjustment for sex and educational attainment a risk reduction of 43% was seen, which persisted in model 3. For colorectal cancer in the second quartile the risk estimates showed a decrease in risk. In the third and fourth quartile of PA a strong risk reduction was found. In model 2 a HR of 0.38(0.20;0.73) for the third and 0.04(0.01;0.31) for the fourth quartile was observed and a linear relationship could be shown.

Table 18 Associations between physical activity and risk of breast cancer. Sensitivity analysis with restriction to cases, that occurred after 3 years of study enrolment. EPIC-Germany (n=45,855)

Breast cancer (cases n=187)					
Non-calibrated - Cambridge index					
	Inactive	Moderately inactive	Moderately active	Active	p-trend
Cases n=	51	65	38	33	
Model 1	1	0.59(0.41;0.85)	0.48(0.32;0.74)	0.55(0.35;0.85)	0.005
Model 2	1	0.58(0.40;0.84)	0.50(0.33;0.77)	0.61(0.39;0.95)	0.021
Model 3	1	0.60(0.41;0.86)	0.53(0.35;0.82)	0.64(0.41;1.01)	0.042
Calibrated – Qb_{AC} [counts/min/day]					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend
Cases n=	59	45	52	31	
Model 1	1	0.84(0.56;1.26)	1.15(0.75;1.75)	0.88(0.52;1.50)	1.000
Model 2	1	0.81(0.54;1.22)	0.96(0.62;1.49)	0.57(0.33;1.00)	0.133
Model 3	1	0.78(0.49;1.22)	0.90(0.53;1.54)	0.51(0.25;1.05)	0.159

Model 1 – not adjusted
Model 2 – adjusted for educational attainment (none, primary school completed, technical/professional school, secondary school, longer education) stratified by age
Model 3 – adjusted for sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50g/day, ≥50<100g/day, ≥100<150g/day ≥150g/day), vegetable intake (<100g/day, ≥100<200g/day, ≥200<300g/day ≥300g/day), red meat intake (<30g/day, ≥30<60g/day, ≥60<90g/day ≥90g/day), alcohol intake (<5g/day, ≥5<10g/day, ≥10<15g/day, ≥15<20g/day ≥20g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), vitamin use (yes/no), mineral use (yes, no), stratified by age

Table 19 Associations between physical activity and risk of colorectal cancer. Sensitivity analysis with restriction to cases, that occurred after 3 years of study enrolment. EPIC-Germany (n=45,855)

Colorectal cancer (cases n=106)					
Non-calibrated - Cambridge index					
	Inactive	Moderately inactive	Moderately active	Active	p-trend
Cases n=	32	46	20	8	
Model 1	1	0.76(0.48;1.19)	0.50(0.28;0.87)	0.27(0.12;0.58)	<0.001
Model 2	1	0.73(0.46;1.15)	0.48(0.27;0.84)	0.26(0.12;0.56)	<0.001
Model 3	1	0.77(0.49;1.22)	0.50(0.28;0.88)	0.26(0.12;0.57)	<0.001
Calibrated – Qb_{AC} [counts/min/day]					
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	p-trend
Cases n=	56	34	15	1	
Model 1	1	0.81(0.52;1.27)	0.49(0.26;0.92)	0.06(0.01;0.41)	<0.001
Model 2	1	0.70(0.44;1.10)	0.38(0.20;0.73)	0.04(0.01;0.31)	<0.001
Model 3	1	0.63(0.38;1.04)	0.33(0.16;0.68)	0.03(0.00;0.24)	<0.001

Model 1 – not adjusted
Model 2 – adjusted for sex and educational attainment (none, primary school completed, technical/professional school, secondary school, longer education) stratified by age

Model 3 – adjusted for sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50g/day, ≥50<100g/day, ≥100<150g/day ≥150g/day), vegetable intake (<100g/day, ≥100<200g/day, ≥200<300g/day ≥300g/day), red meat intake (<30g/day, ≥30<60g/day, ≥60<90g/day ≥90g/day), alcohol intake (<5g/day, ≥5<10g/day, ≥10<15g/day, ≥15<20g/day ≥20g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), vitamin use (yes/no), mineral use (yes, no), stratified by age

7. Discussion *

7.1 Discussion of methods

7.1.1 Study design

In the present doctoral thesis, a prospective cohort design was accomplished to investigate the associations between PA and chronic disease risk and a cross-sectional design was used for calibration. The main strengths of the study were the large study populations used for each of the study parts.

For the index development a study population of 1,344 participants with an objective PA measurement was available. Similarly an internal validation sample of 1,339 participants for the calibration study was used. An internal dataset is the first choice design for calibration studies as the measurement techniques, covariate structure and covariate availability, are the same. This allows a greater precision in estimating the measurement error.

A prospective cohort design consisting of 45,855 consisting of participants from Potsdam and Heidelberg was available for the risk analyses. The prospective cohort design is the most appropriate method to assess the risk of diseases that occur within a specific follow-up period. Since the exposure assessment ensued at the beginning of the study and all prevalent diseases were excluded for the analysis, the subsequently developed incident chronic diseases can be directly compared to the exposure level at baseline and therefore the temporal sequence of these relationships can be taken into account.

7.1.2 Exposure and outcome measurement

The 7-day heart rate and acceleration measurement via the Actiheart sensor was reported to be a valid method for measuring the habitual PA (47). This multifunctional device compromises the advantages of heart rate monitoring and accelerometry and therefore balanced the respective disadvantages. The measurement included weekdays and weekends and therefore accounts for variations in the weekly activity patterns. The extensive PAQ included not only different timeframes but also secondary PA determinants like the residency environment (neighborhood) and psychological inhibitors of PA. This allows a deep exploration of the associations with objectively measured PA and the choice of the most fitting question pool.

Unfortunately, such a broad PAQ is time consuming, promoting errors during the filling in. Another limitation is seen in the objective PA measurement itself. Participants might have changed their behavior during the observation, introducing the so-called Hawthorne effect (33). Another source of error in our PA measurement might be seasonal variability in

*In the framework of this thesis, parts of the discussion on the Improved Physical Activity Index have been published by the author in similar text: Wientzek A, Vigl M, Steindor K, Brühmann B, Bergmann MM, Harttig U, Katzke V, Kaaks R, Boeing H. The Improved Physical Activity Index for measuring physical activity in EPIC Germany. PLoS One. 2014 Mar 18;9(3).

performing PA. Two or more measurement time points, few months apart, would be better to account for PA seasonality (52). The objective measurement of PA was conducted 20 years after baseline examination and an assumption was made, that the association between reported PA and objectively measured PA is the same as 20 years ago. This assumption could present a study limitation as it is not possible to rule out that the magnitude of measurement error or proportion of “over- and underestimators” stayed constant through the years. Nevertheless, it is possible to compare the population characteristics, which do not differ between the main study and the sub-study.
AC differ among devices which hampers replicability of this results in studies using different sensors. For the Actiheart, which was used in the present analyses, a value of 25 counts/min/day corresponds to approximately 540 kcal/day of PAEE.

Analyzed outcomes were overall chronic diseases, type 2 diabetes, myocardial infarction, stroke and overall cancer. The disease endpoints were assessed via self-report but afterwards verified by medical records and death certificates or by contacting the patients' treating physician. Chronic diseases development is a continuous process. Particularly cancer develops slowly and its first clinical symptoms occur years after disease initiation (96). In order to take this issue into account an induction period of 3 years was assumed and incident cancer cases that occurred during the first 3 years after study enrollment were excluded. The risk estimates were not substantially altered.

7.1.3 Statistical methods

The IPAI development was a challenging task as a large question pool was available only a few variables were needed for the final index shape. Simultaneously, the valuable information from the questionnaire is valuable and needs to be prepared in a compact way in order to build the index. Therefore, different approaches were used to examine and use all important information provided. After reducing the available data to a number of meaningful scores, further steps (including multiple linear regression with stepwise variable selection) were performed. This method attempts to remove dispensable variables from the model before adding significant ones. The variable range standardization was a compromise, as also the beta-coefficients from the regression analysis could be used for weighting. Nevertheless, the standardization by range is more user-friendly. The resulting index was categorized into five activity level categories, compared to existing indices that have only four categories. The highest category, “very active”, included participants which PA is higher than that of 90% of the sample. This approach enables more detailed relationship estimation.

To find the best model for baseline data calibration different approaches were used and graphically analyzed. The linear approach was not considered as participants with over- and underestimated PA levels would still confound the results. Fractional polynomials presented a linear-like pattern and were therefore also ruled out. The exclusion of all observations not meeting the Coock's D and leverage criterion would have provided a high proportion of explained variance but it would not have been possible to estimate the PA level of the over and underestimated subjects. The cubic spline and the segmented regression were the only methods of choice. As it was possible to define the breaking points via Coock's D and leverage, the decision was made to use segmented regression for calibration.
A limitation concerning the calibration is the fact that the data were not calibrated using the gold standard method – DLW but an alloyed standard which itself carries measurement error. Nevertheless, the chosen method enabled the measurement of a large sample which combined narrows the error structure and gives a more precise estimation. Spiegelman et al. (99) pointed out that using an alloyed gold standard method for correction and thereby falsely assuming that the errors are uncorrelated will still produce less bias than ignoring the error and refrain from calibration.

The DAG- theory was used for confounder selection. Three models were set up based on the results from the DAG approach. The first model was raw i.e. it did not include any additional covariates. The second model included the variable set for the total effect: age, sex and educational attainment. Age was not used in the adjustment set but in the strata statement. This variable set was equal for all outcomes. The total effect adjustment set was the main model as it describes the sum of direct and indirect effects of the exposure on the outcome variable. Therefore, also mediating effects are included in the estimation.
The third model included an adjustment set, specific for the outcome. This set included mediator variables, targeting the estimation of the independent risk – the so called direct effect; although, the mediator variables often have an influence on the outcome that is overlapping with the exposure effect and therefore an estimation of the true direct effect is nearly impossible (96). The third model estimators are therefore treated as an approximation of the direct effect.
Cox proportional hazards regression was used for chronic disease risk estimation and the above mentioned adjustment sets were applied. The Cambridge Index estimates were presented for each activity category, whereas the calibrated PA estimates were presented in quartiles. Following the distribution presented in Figure 12 and the baseline Cambridge Index activity levels in Table 9 it becomes clear that the estimation differences are due to reclassification where quartile assignment shifted some participants in a new category.

7.2 Discussion of results

7.2.1 Development of the Improved Physical Activity Index

The aim of development of a valid PA index that categorizes people according to their activity level has been conducted successfully. As a continuous outcome, the IPAI is linearly correlated with the respondents' amount of movement and can be used in studies aiming to measure PA in individuals. Furthermore, because activity at work is not the major contributor for the index, it is suitable for elderly populations or populations with a high proportion of unemployed or non-working participants.

The IPAI showed moderate correlations with AC (r=0.40-0.43) and PAEE (r=0.33-0.40). A recent systematic review of 130 PAQs showed that the median validity coefficients of existing and new PAQs are 0.30-0.39 and 0.25-0.41, respectively (16). This ranks the IPAI among the top end of available questionnaire indices.

In the EPIC study the RPAQ and the EPIC-PAQ were used for assessing PA. The Cambridge Index showed moderate validity in the present study as well as in the validation study. Nevertheless, after exclusion of employed participants the Spearman correlation decreased to r=0.18 for AC and r= 0.15 for PAEE. The correlation coefficient of the IPAI categories also decreased but showed still a moderate correlation of r=0.34 for AC and r=0.29 for PAEE. This was an expected phenomenon, as the Cambridge Index cross-classifies occupational activity and recreational activity leading most likely to underestimation of the activity level of non-working participants. The IPAI treats occupational activity as one of five items which can counterbalance the lack of PA at work. In the German EPIC study, as a result of the aging study population, almost 50% of the participants are not employed anymore. Therefore, especially for this population, the IPAI represents a good alternative for categorizing elderly, non-working participants, into activity levels and more importantly, not underestimating their activity level.

One of the variables included in the index was weekend evening computer use. Surprisingly, it was not shown to be positively associated with sedentary time. The correlation with AC and PAEE was positive and so was the regression coefficient. It might be possible, that weekend evening computer use is a proxy measure for being active during the weekdays or for socio-economic PA determinants like educational attainment, which has been shown to be positively correlated with maintaining a healthy lifestyle (100) and being physically active (101).

Based on the obtained results the questions from the questionnaire that was used to calculate the IPAI and also questions used for the Cambridge Index calculation and Total Physical Activity Index calculation were filtered out. Thus, the newly composed questionnaire included an EPIC-PAQ part of ten questions about the PA in the last 12 months, as well as a RPAQ part regarding television viewing, computer use and a list of 17 activities with their frequencies, which were undertaken during the last four weeks (Appendix 2). The questionnaire was later on web-enabled. The questionnaire contained 22 questions, which can easily be filled out. Later, a web-enabled version was generated, giving an opportunity to make the data collection faster, more convenient and less error-prone. The questionnaire was already implemented to measure PA in the 6th EPIC-Germany follow-up-round.

7.2.2 EPIC Germany baseline physical activity data calibration

There are two major PA calibration models reported in the literature – one by Ferrari et al. (85) and one by Spiegelman et al (99). Both models were developed while investigating the validity of a PA questionnaire and accounted for repeated measures of PA from the reference measurement method. The instrumental variables are also similar, although Spiegelman included physical fitness in the model, while Ferrari included an accelerometer measurement.

Ferrari et al. (85) used a validation study at the Alberta Cancer Board with 154 subjects. A PA questionnaire, a 7-day activity log and a 7-day accelerometer PA measurement were repeated four times in 12-week intervals. The PA measures were log-transformed. Maximum likelihood methods were used to fit the model under the assumption that model terms were normally distributed. The PA log was chosen to be the “reference measure” with α_R=0 and β_R=1. This resulted in a slope attenuation factor calculation for the PA questionnaire of 0.145 and a variance of 0.076. The authors described the attenuation as substantial and therefore pointed out that a true RR of 2.0 would be estimated as a RR= 1.1.

Spiegelman et al. (99) used data from the Health Professionals Follow-up study including 98 subjects. PA was measured by a PA questionnaire covering the frequency and duration of PA in the last 12 months, expressed by METh/week. The gold standard was defined as PA measured by four one-week activity diaries repeated every four months. Physical fitness was used as an instrumental variable. Log-transformation was not performed, as normal-distribution assumptions were not needed for the used method – method of moments with covariance-variance matrices. The obtained attenuation factor was applied to the risk estimates for colon cancer. The inverse association between PA and colon cancer (RR of

0.88 (95% CI 0.81-0.95)) even strengthened after measurement error correction to a RR of 0.65 (95% CI 0.48-0.88).

Finally Beyler (102) analyzed NHANES PA data from a sample of 1,569 females and fitted the obtained model to a second sample of 1,522 females. The PA measurement included a PA questionnaire covering the activity from the last 30 days and an objective 7-day measurement by the Actigraph accelerometer. Time spent in MVPA for each participant was calculated. Ordinary least squares and estimated generalized least squares were used to develop a preliminary model and the final model with standard errors, respectively. The estimated regression coefficients were fitted to the second sample. The calibrated estimates suggest that the reported MVPA was overestimated. A reported average time spent in MVPA of 33 minutes corresponds to 6 to 11 minutes of true MVPA depending on age and ethnicity.

The most recent publication on measurement error correction was published 2013 by Tooze et al. (103) who used the USDA Automated Multiple-Pass Method Validation study dataset with 433 participants with available data from questionnaires and DLW and applied the estimated measurement error to the Observing Protein and Energy Nutrition (OPEN) study dataset. The ratio of DLW measured TEE to BEE was taken as the “true” PA and was log-transformed. The authors assumed a classical measurement error model for TEE and Berkson error for BEE and presented a solution for a mixture of these errors. A moderate level of attenuation was found, which was higher in men compared to women with λ=0.73 and λ=0.43, respectively.

Compared to the presented literature, the calibration in this thesis is based on a large study population of 1,399 participants with objectively measured PA that were used to fit a large cohort of 53,088 Germans. The objective heart-rate and acceleration PA measurement of 7-days was used to fit by segmented regression methods the baseline questionnaire measurement. Similar to the other authors, after calibration, the RR decreased compared to uncorrected PA risk estimates.

In contrast, Watkinson et al. (104) claimed, that people with a lower BMI, body fat or other health related indicators overestimate their PA. They assume that their PA is sufficient or high. Therefore, the good correlation between some lifestyle exposures and health outcomes may be explained. In fact, all calibration articles, discussed here, showed a risk decrease. In this thesis, BMI was used as instrumental variable, to account for this claim. It could be shown that there is a negative association between BMI and objectively measured PA in all

Coock's D strata, also in the highest stratum, where the proportion of "overestimators" was probably highest.

Other instrumental variables were age and sex. Age was negatively associated with the objectively measured PA. In all strata, PA was shown to decrease with increasing age. This is a known phenomenon (105). Although, it might be possible, that women are less active than men, this could not be confirmed in the calibration analysis. The beta coefficients for sex were negative but not significant in almost all strata. This finding would rather support the thesis, that women and men perform a similar amount of PA but differ in PAEE. An adjustment for fat free mass, in models using PAEE, would remove the sex confounding and thereby give a similar result as in the present thesis (106).

7.2.3 Physical activity and the risk of chronic diseases

The aim of estimating and comparing the associations between calibrated and non-calibrated baseline PA data and risk of overall chronic diseases, type 2 diabetes, myocardial infarction, stroke and overall cancer has been pursued. By comparison of the active compared to the inactive Cambridge Index category a risk reduction from 11% to 43% of all chronic diseases could be shown. The HRs of the calibrated results were more precise, showed a stronger risk reduction (from 28% to 92%) for overall chronic diseases, type 2 diabetes, myocardial infarction and stroke. There were no associations between the calibrated PA and risk of cancer, even after excluding the first 3 years of follow-up.

Type 2 diabetes

As already mentioned in the introduction, there is strong evidence for type 2 diabetes preventive effects of PA. A systematic review by Jeon et al. (60) showed a 30% risk decrease in type 2 diabetes for regular PA of moderate intensity. It included 301,221 participants with 9,367 incident type 2 diabetes cases. The Nurses' Health Study, with 16 years of follow-up and 4,030 incident cases also showed 22-fold risk increase in inactive, abdominal-obese women compared to active abdominally lean women. After leaving out abdominal obesity and comparing only inactive versus active women, a 2.7 risk increase was observed. PA was measured by summing up METh/week of sports activates (walking, jogging, running, bicycling, lap swimming, playing tennis or squash, and participating in calisthenics). The authors reported high questionnaire validity of r=0.79 (correlation with a 1-week PA recall). Similar results were presented for the Physicians' Health Study, where a nearly 7-fold increase in in diabetes type 2 risk for inactive obese men compared to active normal-weight was seen (64).

The EPIC InterAct study, which was established as a case-cohort study of incident type 2 diabetes cases form ten European countries analyzed 15,934 individuals with 778 type 2

diabetes cases (107). PA was measured by questionnaire. Sport and cycling h/week were summed up and individuals were allocated to four activity categories. Inactivity was independently of BMI and abdominal obesity associated with a type 2 diabetes risk increase: HR=1.81 (1.34;2.43) for normal-weight men and 1.50 (1.17;1.93) for normal-weight women. For the centers Potsdam and Heidelberg the HR (95%CI) between a 1-level increase in PA and BMI, education, smoking status, alcohol consumption and energy intake adjusted type 2 diabetes risk, were 0.62 (0.51;0.74) and 0.80 (0.66;0.95) in women and 0.91 (0.76;1.09) and 0.88 (0.71;1.08) in men, respectively.

The literature results are in concordance with the results of the present thesis; nevertheless, the risk estimates in previous studies showed a somewhat weaker relationship. The non-calibrated PA risk for type 2 diabetes for both centers (top versus bottom) was HR=0.57(0.48-0.67). After calibration the risk reduction increased, suggesting a 92% total effect of PA risk reduction for type 2 diabetes. After adjusting for confounders, still a 60% independent risk reduction could be found, for both: Potsdam and Heidelberg. The differences in risk estimates may be due to calibration, where some participants (most likely “under- and over-estimators”), who were categorized as active by the Cambridge Index, were shifted towards the mean.

Myocardial infarction

PA and risk of CHD was widely studied. Nevertheless, studies with particular focus on MI are lacking. A recent meta-analysis by Li and Siegrist (108) on PA and CVD risk reviewed articles from 1980 to 2010 and included 11 prospective cohort studies on CHD risk and leisure time PA. The overall RR (95%CI) in men was 0.79 (0.73;0.85) and in women was 0.71 (0.65;0.77) comparing the highest PA category with the lowest.

Elosua et al. (109) aimed to find a dose-response relationship between PA and risk of MI, using a case-control study design with 1,339 cases and 1,339 controls. The Minnesota PA questionnaire was administered to assess TEE in PA and in light-, moderate-, and high-intensity PA. The main finding was a non-linear relationship between PA and MI risk. Lower MI odds were observed at low PA intensities of 500 MET minutes/week. The lowest MI odds were observed at 1500 MET minutes/week.

A linear relationship between PA and CHD risk was shown in 7,307 male participants of the Harvard Alumni Health Study who answered a questionnaire on walking, stain climbing and engaging in recreational activities in the last week (70). The authors reported high validity of r=0.65 with a PA record. PAEE was estimated and five PAEE categories were set up: <1000 kcal, 1000-2000 kcal, 2000-3000 kcal, 3000-4000 kcal, 4000-5000 kcal and >5000 kcal per week. The age and exercise duration adjusted RR for CHD, compared to the lowest PA

category (<1000 kcal/week) decreased in every further category by 24%, 25%, 25% to 34%, respectively.

The uncorrected HRs in the present thesis were favoring a non-linear relationship between PA and MI. The risk decreases in the moderately inactive group, increases in the moderately active and is lowest in the active group with a 38% MI risk reduction. In the calibrated analyses a linear trend can be found, decreasing the risk for MI by 13%, 18% and 60% in the second, third and fourth Qb_{AC} quartile compared to the first. After performing the center-stratified analysis it became clear that the results were triggered by the Heidelberg center, where even a 77% MI risk decrease in the fourth PA quartile could be seen. Very wide confidence intervals in the Potsdam center made the center specific interpretation difficult.

Stroke

Leisure time PA has been shown to be associated with total stroke risk in a meta-analysis of 31 publications including cohort and case-control studies (75). A 22% risk reduction could be found between the inactive and active category. After differentiating between hemorrhagic stroke and ischemic stroke, the estimates became more precise. A risk reduction of 26% and 21% was shown, respectively. Schnohr et al. (110) who did not differentiate between stroke types, reported a non-significant association between stroke mortality risk and PA, although a risk reducing trend was seen in the moderately active group compared to inactive (RR=0.64 (0.39;1.05)). A similar finding reported Huerta et al. (76) in EPIC-Spain, where a risk reduction in women of 33-55% was observed when comparing the recreational PA of moderate intensity groups with the inactive participants. In both studies PA was measured by questionnaire.

The relationship between the Cambridge Index (non-calibrated) and the risk of stroke showed a preventive effect of PA in the moderately inactive and moderately active category with a risk decrease of 20% to 36%. In the highest PA category a slight risk decrease could be seen, although the risk estimates were characterized by large confidence intervals. On the other hand, the calibrated results with Qb_{AC} as measure of PA showed no association in the second and third quartile compared to the first, but a 46% risk decrease in the highest quartile. Similar to the results for type 2 diabetes, this indicates that calibration shifted "under- and over estimators" towards the mean, and the calculated association approximates closer to the true value.

Cancer

Cancer is a complex disease and therefore, studies examining the relationship between PA and cancer risk, study it separately for different cancer types. Nevertheless, this was not possible in the scope of this thesis.

A review conducted by Anzuini et al. (111), that included meta-analyses and original articles, presented evidence for associations between PA and different cancer types. A risk reduction of 13-14% for colorectal cancer, and 46% of breast cancer could be found. Also lung cancer has been highlighted as being reduced by heavy leisure time PA. The authors claimed, that occupational activities, that are stressful, can partly counteract the beneficial effect of PA on cancer risk (112).

As mentioned in the introduction, in the EPIC study a relationship between PA and colon cancer risk was found (80). More than 413,000 participants were examined and followed over more than six years, while 1,094 colon cancer cases occurred. PA was measured by questionnaire and the Total Physical Activity Index was calculated. The age and center stratified HR suggested a 24% risk decrease in active compared to inactive individuals. Center specific data was not available as there was no heterogeneity. In the same cohort, the risk for ovarian cancer was examined (113). 731 cases occurred. In the model adjusted for known risk factors a higher risk of ovarian cancer with higher PA was shown. In the active category, compared to the inactive a HR of 1.32 (0.93-1.88) was found. The authors stated that measurement error is likely to be the cause of the statistical attenuation, but in the opinion of the author of this thesis, this may be only partly true and is rather an attempt to discuss a non-public health conform message.

A lung cancer risk study by Steindorf et al. (114) in EPIC with 1,083 cases, that used the same Total Physical Activity Index, has shown a detrimental effect of PA on lung cancer risk. Only sports activity in men and cycling in women showed a protective effect. No center specific estimates were shown. There are other studies on lung cancer and PA that observed different findings. A 22% lung cancer risk decrease was shown by Leitzmann et al. (115), who analyzed data from 501,148 participants of the National Institutes of Health–AARP Diet and Health Study. Also a meta-analysis of prospective cohort-studies showed a consistent beneficial effect of high and medium levels PA (116). The combined estimate suggested a lung cancer risk reduction of 13% for moderate and 23% for high PA compared to inactivity. Therefore, it is possible that the lung cancer risk results from the EPIC Study are the result of using the Total Physical Activity Index for PA level classification which is, as already highlighted, a compromised measure of PA (r=0.05) and was reported to show high heterogeneity (4).

For the comparison purposes of this discussion, the model 2 HR for the overall cancer risk and the Total Physical Activity Index were calculated to be 0.90 (0.75;1.08) between active and inactive. Overall cancer risk among the non-calibrated results in the present thesis was shown to be slightly decreased in all Cambridge Index categories from 11 to 13%. The calibrated PA HR could not confirm this finding. A slight risk increase was found in the highest quartile, in the raw model (1.13 (0.96;1.33)) and the sex, educational attainment

adjusted model 2 (1.10 (0.93;1.31)), and in the center stratified analysis. Although, the confidence intervals were wide, this is rather leading to a no-association conclusion. A possible explanation of this null result may be the long latency of cancer. Therefore, a sensitivity analysis was performed, excluding cases which have been reported within the first three years of follow-up. It revealed that there was a strong positive confounding by sex, age and educational attainment in the first model that introduced a linear risk increase in the PA categories, up to 47%. After adjustment a slight risk reducing effect could be observed in the second and third quartile. Based on these results it is not possible to issue any recommendations. A cancer type stratified analysis using the calibrated data would give answers if there is any relationship between particular cancer types and PA. In order to address this issue an analysis for two cancer types was performed which were shown in literature to be associated with PA – colon cancer and breast cancer. The non-calibrated results showed a persisting preventive association between both breast and colorectal cancer. The calibrated HR showed only an association with the highest activity quartile for breast cancer, suggesting that only high PA is having a preventive effect on the risk of breast cancer. This would be in favor of the biological mechanisms that might underlay this relationship which imply that PA works by reducing the luteal phase, lengthening the menstrual cycle and delaying the age at menarche in women (83). For colorectal cancer a risk reduction similar to type 2 diabetes was found. People, who engage in 75% more PA than the rest of the population, had a 96% lower risk to develop colorectal cancer. This relationship is still persistent after adjusting for potential mediators suggesting that the total effect of PA is the same as the direct effect. The fact that a linear association through all PA quartiles was found suggests that even light or moderate PA have a risk reducing effect on colorectal cancer development. The underlying biological mechanism implies that this effect is due to a shortening of the gastrointestinal transit time, the reduction of systemic inflammation or increased levels of Prostaglandin F, which increases gut motility (11).

8. Conclusions and public health implications

In conclusion, the aim of this thesis of developing a valid physical activity index, which is able to categorize people into activity categories and can be used as a continuous measure, was achieved. The Index was enabled designing a PAQ that can be used as a baseline tool, as well as for follow-up study PA measurement. Furthermore, because in populations with a high rate of non-working participants (likely in EPIC-Germany) the performance of the IPAI is significantly better than the established indices, the use of the IPAI in the future EPIC-Germany follow-ups is proposed.

Furthermore, the calibration procedure helped to identify participants who most likely over- or underestimated their PA level and made the estimation of PA on chronic disease risk more precise. The use of AC for calibration eliminated confounding by weight and sex from the estimates. Data calibration techniques are helpful tools and should be used in future studies focusing on subjective PA measurement methods in order to enhance the estimates. Public health initiatives rely on epidemiological studies aiming to quantify the relationships between PA and chronic diseases. Therefore, an accurate PA measurement is crucial in order to meet the requirements of public health policy.

PA is a lifestyle factor with strong preventive properties especially for type 2 diabetes and colorectal cancer. The result suggests that nine of ten Germans that are more active than 75% of the rest of the population can prevent the development of type 2 diabetes and colorectal cancer. The linear relationship points towards a commonly known conclusion – even light and moderate PA counts in type 2 diabetes and colorectal cancer prevention. It is a public message that reveals the importance of PA in disease development. Furthermore it shows how measurement error in public health can affect the results and how important it is to account for it.
MI, stroke and breast cancer risk can also be reduced by PA. The relationship is was strongest among the most active participants. Therefore, PA of at least moderate intensity should be recommended for those diseases. Further investigation on PA and the risk of particular cancer types using calibrated data in the EPIC-Germany sample is needed.

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Abstract

Physical activity (PA) is a lifestyle factor that has been shown to prevent chronic diseases. The accurate PA measurement is essential to estimate the true magnitude of the relationship between PA and disease risk. Nowadays, objective measurement methods for PA have been developed and improve the challenging task of measuring the individuals' PA level. Therefore, the aims of this thesis were firstly, the development and evaluation of a valid physical activity index – the Improved Physical Activity Index (IPAI), which will be able to categorize people into activity categories but may also be used as a continuous measure that reflects one's activity amount (movement). Secondly, the calibration of the available baseline PA questionnaire measurement and finally, the estimation of the associations between calibrated and non-calibrated baseline PA data and risk of overall chronic diseases, type 2 diabetes, myocardial infarction, stroke and overall cancer.

These objectives were accomplished by applying an extensive physical activity questionnaire and a 7-day heart rate and acceleration sensor PA measurement to a sub-sample (n=1,615) of older adults from the European Prospective Investigation into Cancer and Nutrition (EPIC-Germany) study. Baseline self-reported PA was calibrated using statistical models based on the objective PA measurement in the sub-sample. The risk of chronic diseases was estimated using Cox proportional hazards regression in the whole EPIC-Germany cohort.

The IPAI consists of items covering five areas including PA at work, sport, cycling, television viewing, and computer use. The correlations between the IPAI and accelerometer counts in the training and validation sample ranged from r=0.39 to 0.44 and with physical activity energy expenditure from r=0.32 to 0.40 and were higher than between the Cambridge Index or the Total Physical Activity Index with the objective measures. In non-working participants the IPAI also showed higher correlations than the established indices.

For the baseline PA data calibration segmented regression analysis has been chosen.

The hazard rates (HR (95% confidence intervals)) for the risk reduction in the highest calibrated PA category compared to the lowest for overall chronic diseases HR=0.40(0.35-0.46), type 2 diabetes HR=0.08(0.06-0.10), myocardial infarction HR=0.40(0.24-0.67) and stroke HR=0.54(0.33-0.87) were lower than the non-calibrated results HR=0.72(0.66-0.80), HR=0.57(0.48-0.67), HR=0.62(0.44-0.88), and HR=0.86(0.62-1.19), respectively. There were no associations between the calibrated PA and risk of cancer, even after excluding the first 3 years of follow up.

In conclusion, a valid PA index which is able to express PA on a continuous scale as well as to categorize participants was developed. In populations with increasing rates of non-working people the performance of the IPAI is better than the established indices used in EPIC.
The PA data calibration provides more precise risk estimates. The preventive effects of PA on overall chronic disease risk, type 2 diabetes, myocardial infarction and stroke, has been shown to be underestimated. Public health interventions should persistently focus on PA, especially in type 2 diabetes jeopardized individuals.

Deutsche Zusammenfassung

Körperliche Aktivität (KA) ist ein Lifestyle Faktor, der vor chronischen Erkrankungen zu schützen scheint. In der European Prospective Investigation into Cancer and Nutrition (EPIC)-Studie wurden zwei Fragebögen verwendet, mit denen anhand des Cambridge Indexes und des Total Physical Activity Indexes die KA der Teilnehmer kategorisiert werden kann. Die präzise Messung der PA ist essentiell, um die wahre Assoziationsstärke zwischen KA und chronischen Erkrankungen zu schätzen. Objektive Messmethoden, die heutzutage zum Einsatz kommen, vereinfachen die schwierige Aufgabe der präzisen Messung der KA. Basierend darauf, wurden die folgenden Ziele in dieser Doktorarbeit verfolgt: die Entwicklung und Evaluierung eines validen KA Indexes– den Improved Physical Activity Index (IPAI), welcher in der Lage sein soll, die KA der Personen zu kategorisieren aber auch eine kontinuierliche Messung der KA zu liefern. Diese soll das Bewegungsausmaß widerspiegeln. Des Weiteren wurde eine Kalibrierung der Basis Fragebogen-Daten zur PA und die Schätzung des Zusammenhangs zwischen nicht-kalibrierter und kalibrierter KA und chronischen Erkrankungen, Typ 2 Diabetes, Myokardinfarkt, Schlaganfall und Krebs, angestrebt.

Diese Ziele wurden in den deutschen EPIC-Zentren Potsdam und Heidelberg verfolgt. In einer Substudie wurden 1615 Teilnehmer rekrutiert. Diese Substudie beinhaltete ein breites Fragenspektrum zur üblichen KA, sowie eine objektive 7-Tage Messung der KA mittels eines Herzfrequenz und Bewegungsmessers - Actiheart. Die Baseline Fragebogenangaben zur KA wurden, mittels der aus der Substudie gewonnenen Daten, kalibriert. Das Risiko für chronische Erkrankungen wurde in der Gesamtkohorte mit Hilfe von proportionaler Hazards-Regression nach Cox berechnet.

Der IPAI besteht aus den folgenden Aktivitätsvariablen: Art der Berufstätigkeit, Fahrrad fahren (Stunden/Woche), dem Sporthäufigkeitsscore, sowie Fernsehscore und Computernutzung (Stunden/Wochenende ab 18Uhr). Korrelationen zwischen dem IPAI und objektiv gemessener KA betrugen r=0.39-0.44 für Aktivitätscounts und r=0.32-0.40 für Aktivitätsenergieausgabe (PAEE). Der Cambridge Index und der Total Physical Activity Index waren schwächer mit objektiv gemessener KA korreliert als der IPAI. In nicht-berufstätigen Teilnehmern war der IPAI auch stärker mit objektiv gemessener KA korreliert, als die bisher genutzten Indizes.

Stückweise Regression wurde zur Kalibrierung der Baseleine KA Daten angewandt.

In den kalibrierten Daten waren die Hazardraten (HR (95% Konfidenzeinterval)) zwischen der höchsten KA Kategorie, im Vergleich zur niedrigsten KA Kategorie, niedriger als in den

nicht kalibrierten Daten für die meisten chronischen Erkrankungen HR=0.40(0.35-0.46), Typ 2 Diabetes HR=0.08(0.06-0.10), Myokardinfarkt HR=0.40(0.24-0.67) und Schlaganfall HR=0.54(0.33-0.87). Die nicht-kalibrierten HRs betragen, in der gleichen Reihenfolge: HR=0.72(0.66-0.80), HR=0.57(0.48-0.67), HR=0.62(0.44-0.88), und HR=0.86(0.62-1.19), Es wurden keine Zusammenhänge zwischen KA und Krebs gefunden, auch nicht nach Ausschluss von Erkrankungen, die in den ersten 3 Jahren der Nachbeobachtung aufgetreten sind.

Zusammenfassend zeigen die vorliegenden Ergebnisse, dass der IPAI ein valides Instrument zur populationsbezogenen subjektiven Messung der üblichen KA/Bewegung (sowohl kontinuierlich als auch in Kategorien) ist und in Studien zu diesem Zweck angewandt werden kann.

Die Datenkalibrierung liefert eine präzisere Schätzung des Zusammenhangs zwischen KA und chronischen Erkrankungen. Die präventiven Effekte von KA auf chronische Erkrankungen, Typ 2 Diabetes, Myokardinfarkt und Schlaganfall werden in Studien mit Fragebogenmessung der KA unterschätzt. Interventionen im Bereich Public Health, vor allem in der Gruppe von Typ 2 Diabetes Gefährdeten, sollten einen stärkeren Fokus auf KA legen.

Supplementary material

Appendix 1

EPIC-Germany baseline physical activity variables:

PA at work

Cambridge Index

Total Physical Activity Index

Sweating (yes/no)

Type of PA at work

Number of hours watching television/week

Walking in summer (h/week)

Walking in winter (h/week)

Cycling in summer (h/week)

Cycling in winter (h/week)

Gardening in summer (h/week)

Gardening in winter (h/week)

Do-it-yourself activities (h/week)

Physical exercise in summer (h/week)

Physical exercise in winter (h/week)

Housework (h/week)

Number of floors of stairs climbed /day

Practice of vigorous PA

Appendix 2

Körperliche Aktivität in den vergangenen 12 Monaten

Stellen Sie sich eine für Sie typische Woche der letzten 12 Monate vor und geben Sie an, wie viele Stunden pro Woche Sie im Durchschnitt die folgenden Aktivitäten ausgeübt haben. (Sommer gilt von April bis September und Winter von Oktober bis März.)

Wie viele Stunden verbrachten Sie durchschnittlich mit folgenden Tätigkeiten?

Zu Fuß gehen (Spazieren gehen, Weg zur Arbeit, Einkaufen gehen)	◯ Nie				
	Im Sommer pro Woche	☐☐	Stunden	☐☐	Minuten
	Im Winter pro Woche	☐☐	Stunden	☐☐	Minuten
Radfahren (Spazieren fahren, Weg zur Arbeit, Einkaufen fahren)	◯ Nie				
	Im Sommer pro Woche	☐☐	Stunden	☐☐	Minuten
	Im Winter pro Woche	☐☐	Stunden	☐☐	Minuten
Sport treiben (außer Rad fahren oder Gehen wie oben angegeben)	◯ Nie				
	Im Sommer pro Woche	☐☐	Stunden	☐☐	Minuten
	Im Winter pro Woche	☐☐	Stunden	☐☐	Minuten
Gartenarbeit	◯ Nie				
	Im Sommer pro Woche	☐☐	Stunden	☐☐	Minuten
	Im Winter pro Woche	☐☐	Stunden	☐☐	Minuten
Handwerkliche Arbeiten am Haus oder in der Wohnung	◯ Nie				
	ganzjährig pro Woche	☐☐	Stunden	☐☐	Minuten
Hausarbeit (Kochen, Waschen, Putzen etc.)	◯ Nie				
	ganzjährig pro Woche	☐☐	Stunden	☐☐	Minuten
Fernsehen	◯ Nie				
	Im Sommer pro Woche	☐☐	Stunden	☐☐	Minuten
	Im Winter pro Woche	☐☐	Stunden	☐☐	Minuten
Schlafen (tagsüber)	◯ Nie				
	Im Sommer pro Woche	☐☐	Stunden	☐☐	Minuten
	Im Winter pro Woche	☐☐	Stunden	☐☐	Minuten
Schlafen (nachts)	◯ Nie				
	Im Sommer pro Woche	☐☐	Stunden	☐☐	Minuten
	Im Winter pro Woche	☐☐	Stunden	☐☐	Minuten
Wie viele Treppen stiegen Sie durchschnittlich in den vergangenen 12 Monaten pro Tag hinauf?	☐☐ Stockwerke pro Tag				
	◯ Keine Treppen				

Die folgenden Fragen richten sich auf Ihre alltäglichen Aktivitäten zu Hause und das Sporttreiben in den vergangenen 4 Wochen

TV, DVD oder Video sehen: Wie viele Stunden pro Tag haben Sie durchschnittlich in den vergangenen 4 Wochen mit Fernsehen, DVD- und Videosehen verbracht?

an Werktagen vor 18 Uhr	◯ Nie
	◯ Weniger als 1 Stunde pro Tag
	◯ 1 bis weniger als 2 Stunden pro Tag
	◯ 2 bis weniger als 3 Stunden pro Tag
	◯ 3 bis weniger als 4 Stunden pro Tag
	◯ 4 und mehr Stunden pro Tag
an Werktagen nach 18 Uhr	◯ Nie
	◯ Weniger als 1 Stunde pro Tag
	◯ 1 bis weniger als 2 Stunden pro Tag
	◯ 2 bis weniger als 3 Stunden pro Tag
	◯ 3 bis weniger als 4 Stunden pro Tag
	◯ 4 und mehr Stunden pro Tag

TV, DVD oder Video sehen: Wie viele Stunden pro Tag haben Sie durchschnittlich in den vergangenen 4 Wochen mit Fernsehen, DVD- und Videosehen verbracht?

an Wochenendtagen vor 18 Uhr
- ◯ Nie
- ◯ Weniger als 1 Stunde pro Tag
- ◯ 1 bis weniger als 2 Stunden pro Tag
- ◯ 2 bis weniger als 3 Stunden pro Tag
- ◯ 3 bis weniger als 4 Stunden pro Tag
- ◯ 4 und mehr Stunden pro Tag

an Wochenendtagen nach 18 Uhr
- ◯ Nie
- ◯ Weniger als 1 Stunde pro Tag
- ◯ 1 bis weniger als 2 Stunden pro Tag
- ◯ 2 bis weniger als 3 Stunden pro Tag
- ◯ 3 bis weniger als 4 Stunden pro Tag
- ◯ 4 und mehr Stunden pro Tag

Gebrauch des Computers, nicht während der Arbeitszeit (z.B. Internet, Email, Playstation, Xbox, Gameboy):

Wie viele Stunden pro Tag haben Sie durchschnittlich in den vergangenen 4 Wochen den Computer außerhalb der Arbeit z.B. zu Hause genutzt?

an Werktagen vor 18 Uhr
- ◯ Nie
- ◯ Weniger als 1 Stunde pro Tag
- ◯ 1 bis weniger als 2 Stunden pro Tag
- ◯ 2 bis weniger als 3 Stunden pro Tag
- ◯ 3 bis weniger als 4 Stunden pro Tag
- ◯ 4 und mehr Stunden pro Tag

Gebrauch des Computers, nicht während der Arbeitszeit (z.B. Internet, Email, Playstation, Xbox, Gameboy):

an Werktagen nach 18 Uhr
- ◯ Nie
- ◯ Weniger als 1 Stunde pro Tag
- ◯ 1 bis weniger als 2 Stunden pro Tag
- ◯ 2 bis weniger als 3 Stunden pro Tag
- ◯ 3 bis weniger als 4 Stunden pro Tag
- ◯ 4 und mehr Stunden pro Tag

an Wochenendtagen vor 18 Uhr
- ◯ Nie
- ◯ Weniger als 1 Stunde pro Tag
- ◯ 1 bis weniger als 2 Stunden pro Tag
- ◯ 2 bis weniger als 3 Stunden pro Tag
- ◯ 3 bis weniger als 4 Stunden pro Tag
- ◯ 4 und mehr Stunden pro Tag

an Wochenendtagen nach 18 Uhr
- ◯ Nie
- ◯ Weniger als 1 Stunde pro Tag
- ◯ 1 bis weniger als 2 Stunden pro Tag
- ◯ 2 bis weniger als 3 Stunden pro Tag
- ◯ 3 bis weniger als 4 Stunden pro Tag
- ◯ 4 und mehr Stunden pro Tag

Fortbewegung (außer Arbeitsweg)

Wie haben Sie sich in den vergangenen 4 Wochen am häufigsten fortbewegt? Der Weg zur Arbeit soll hier nicht berücksichtigt werden.
- ◯ Zu Fuß
- ◯ Mit dem Fahrrad
- ◯ Mit öffentlichen Verkehrsmitteln
- ◯ Mit dem Auto oder Motorrad

Nachfolgend finden Sie Sportarten aufgeführt, von denen wir wissen möchten, ob und wie oft Sie sie in den **vergangenen 4 Wochen** ausgeübt haben.		
Radfahren (nicht zur Fortbewegung)	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	
Gymnastik (z.B. Yoga, Tai-Chi, Qi-Gong, Pilates, Entspannungsübungen, Bodengymnastik, Wassergymnastik)	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	
Schwimmen	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	
Spazierengehen (nicht zur Fortbewegung) Nordic Walking	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	
Fitness (z.B. Zirkeltraining, Aerobic, Step-Aerobic, Power-Gymnastik)	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	

Weitere Sportarten		
Laufen als Wettkampfsport	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	
Joggen	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	
Wandern, Bergwandern	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	
Krafttraining (z.B. Bodybuilding, Hanteltraining, Kiesertraining)	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	
Konditionstraining, Heimtrainer (z.B. Fahrrad- oder Rudergerät)	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	
Rehasport (z.B. Rückensport, Goalball, Lungensport, Asthmasport, Rollstuhltanz, Rollstuhlsport)	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	

Weitere Sportarten		
Tanzen	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	
Ballsport (z.B. Fußball, Volleyball, Basketball, Handball)	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	
Kegelsport (z.B. Kegeln, Bowling, Boule, Bosseln, Dart)	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	
Tennis, Badminton, Federball	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	
Skilanglauf, Skiabfahrt, Snowboard	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	

andere Sportart: (bitte nennen)		
	◯ Nie	◯ 2-3 mal wöchentlich
	◯ 1 mal in 4 Wochen	◯ 4-5 mal wöchentlich
	◯ 2-3 mal in 4 Wochen	◯ Täglich
	◯ 1 mal wöchentlich	

Absichten, sportlich aktiv zu werden

Wenn Sie derzeitig regelmäßig sportlich aktiv sind, lassen Sie den folgenden Abschnitt bitte frei.

Wenn Sie derzeitig **nicht** regelmäßig sportlich aktiv sind, geben Sie bitte an, welche der nachfolgenden Aussagen auf Sie zutrifft (bitte nur eine Antwort ankreuzen)	◯ Eine regelmäßige sportliche Aktivität ist mir wegen einer körperlichen Behinderung nicht möglich.
	◯ Ich habe **nicht** vor, in den nächsten 6 Monaten regelmäßig sportlich aktiv zu werden.
	◯ Ich habe vor, in den nächsten 6 Monaten (wieder) regelmäßig sportlich aktiv zu werden.
	◯ Ich habe vor, in den nächsten 30 Tagen (wieder) regelmäßig sportlich aktiv zu werden.

Wenn Sie sich **nicht** mit dem Gedanken tragen, körperlich aktiver zu werden, lassen diesen Abschnitt bitte frei.

Wenn Sie sich mit dem Gedanken tragen, körperlich aktiver zu werden: Haben Sie schon etwas unternommen, z.B. ein Sportgerät oder Sportkleidung gekauft, sich nach einem Sportverein erkundigt, schon einmal probiert, Sport zu treiben?	◯ Nein, ich habe Nichts unternommen.
	◯ Ja, ich habe etwas unternommen.
	Bitte angeben:

Möchten Sie zum Schluss noch etwas ergänzen?

Appendix 3

Supplementary table 1 Center specific associations between Questionnaire-based acceleration counts (Qb_{AC}) and overall chronic disease risk in EPIC-Germany (n=45,855)

Chronic diseases	Qb_{AC} [counts/min/day] Heidelberg (cases n=2,130)			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Cases n=	793	601	472	264
Model 1	1	0.69(0.62;0.76)	0.59(0.53;0.67)	0.44(0.37;0.51)
Model 2	1	0.65(0.59;0.73)	0.57(0.50;0.64)	0.42(0.36;0.49)
Model 3	1	0.76(0.67;0.86)	0.71(0.61;0.83)	0.60(0.48;0.74)
	Potsdam (cases n=2,378)			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Cases n=	1274	661	291	152
Model 1	1	0.68(0.61;0.75)	0.41(0.35;0.48)	0.33(0.27;0.42)
Model 2	1	0.67(0.60;0.74)	0.41(0.35;0.48)	0.34(0.27;0.42)
Model 3	1	0.85(0.76;0.95)	0.63(0.53;0.75)	0.64(0.50;0.83)

Model 1 – not adjusted
Model 2 – adjusted for sex and educational attainment (none, primary school completed, technical/professional school, secondary school, longer education) stratified by age
Model 3 – adjusted for sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50g/day, ≥50<100g/day, ≥100<150g/day ≥150g/day), vegetable intake (<100g/day, ≥100<200g/day, ≥200<300g/day ≥300g/day), red meat intake (<30g/day, ≥30<60g/day, ≥60<90g/day ≥90g/day), alcohol intake (<5g/day, ≥5<10g/day, ≥10<15g/day, ≥15<20g/day ≥20g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), vitamin use (yes/no), mineral use (yes, no), stratified by age

Supplementary table 2 Center specific associations between Questionnaire-based acceleration counts (Qb_{AC}) and type 2 diabetes risk in EPIC-Germany (n=45,855)

Type 2 diabetes	Qb_{AC} [counts/min/day] Heidelberg (cases n=717)			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Cases n=	389	197	95	36
Model 1	1	0.43(0.36;0.51)	0.21(0.17;0.26)	0.10(0.07;0.14)
Model 2	1	0.40(0.33;0.47)	0.19(0.15;0.24)	0.09(0.06;0.13)
Model 3	1	0.70(0.57;0.86)	0.48(0.36;0.64)	0.39(0.25;0.61)
	Potsdam (cases n=888)			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Cases n=	566	226	72	24
Model 1	1	0.38(0.32;0.45)	0.12(0.09;0.16)	0.06(0.04;0.09)
Model 2	1	0.38(0.32;0.45)	0.12(0.09;0.16)	0.06(0.04;0.09)
Model 3	1	0.77(0.64;0.93)	0.43(0.31;0.58)	0.39(0.23;0.64)

Model 1 – not adjusted
Model 2 – adjusted for sex and educational attainment (none, primary school completed, technical/professional school, secondary school, longer education) stratified by age
Model 3 – adjusted for sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50g/day, ≥50<100g/day, ≥100<150g/day ≥150g/day), vegetable intake (<100g/day, ≥100<200g/day, ≥200<300g/day ≥300g/day), red meat intake (<30g/day, ≥30<60g/day, ≥60<90g/day ≥90g/day), alcohol intake (<5g/day, ≥5<10g/day, ≥10<15g/day, ≥15<20g/day ≥20g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), stratified by age.

Supplementary table 3 Center specific associations between Questionnaire-based acceleration counts (Qb_{AC}) and risk of myocardial infarction in EPIC-Germany (n=45,855)

Myocardial infarction	Qb_{AC} [counts/min/day] Heidelberg (cases n=180)			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Cases n=	63	53	51	13
Model 1	1	0.75(0.52;1.09)	0.79(0.54;1.16)	0.28(0.15;0.53)
Model 2	1	0.68(0.47;1.00)	0.72(0.48;1.07)	0.27(0.14;0.52)
Model 3	1	0.79(0.52;1.20)	0.92(0.56;1.51)	0.39(0.18;0.88)
	Potsdam (cases n=191)			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Cases n=	89	64	30	8
Model 1	1	1.11(0.78;1.58)	0.85(0.52;1.41)	0.55(0.24;1.28)
Model 2	1	1.12(0.78;1.60)	0.99(0.59;1.65)	0.82(0.34;1.96)
Model 3	1	1.42(0.96;2.08)	1.49(0.84;2.64)	1.51(0.59;3.90)

Model 1 – not adjusted
Model 2 – adjusted for sex and educational attainment (none, primary school completed, technical/professional school, secondary school, longer education) stratified by age
Model 3 – adjusted for sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50g/day, ≥50<100g/day, ≥100<150g/day ≥150g/day), vegetable intake (<100g/day, ≥100<200g/day, ≥200<300g/day ≥300g/day), red meat intake (<30g/day, ≥30<60g/day, ≥60<90g/day ≥90g/day), alcohol intake (<5g/day, ≥5<10g/day, ≥10<15g/day, ≥15<20g/day ≥20g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), stratified by age

Supplementary table 4 Center specific associations between Questionnaire-based acceleration counts (Qb_{AC}) and stroke risk in EPIC-Germany (n=45,855)

Stroke	Qb_{AC} [counts/min/day] Heidelberg (cases n=164)			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Cases n=	46	55	47	16
Model 1	1	1.14(0.76;1.69)	1.06(0.69;1.63)	0.45(0.24;0.84)
Model 2	1	1.10(0.74;1.65)	1.06(0.69;1.64)	0.47(0.25;0.89)
Model 3	1	1.11(0.91;1.72)	1.04(0.61;1.79)	0.45(0.20;1.02)
	Potsdam (cases n=178)			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Cases n=	85	55	26	12
Model 1	1	1.03(0.71;1.49)	0.81(0.48;1.39)	0.56(0.25;1.26)
Model 2	1	1.06(0.72;1.54)	0.85(0.49;1.48)	0.64(0.28;1.49)
Model 3	1	1.14(0.75;1.72)	0.96;0.52;1.95)	0.75(0.29;1.95)

Model 1 – not adjusted
Model 2 adjusted for sex and educational attainment (none, primary school completed, technical/professional school, secondary school, longer education) stratified by age
Model 3 – adjusted for sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50g/day, ≥50<100g/day, ≥100<150g/day ≥150g/day), vegetable intake (<100g/day, ≥100<200g/day, ≥200<300g/day ≥300g/day), red meat intake (<30g/day, ≥30<60g/day, ≥60<90g/day ≥90g/day), alcohol intake (<5g/day, ≥5<10g/day, ≥10<15g/day, ≥15<20g/day ≥20g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), stratified by age

Supplementary table 5 Center specific associations between Questionnaire-based acceleration counts (Qb_{AC}) and overall cancer risk in EPIC-Germany (n=45,855)

Overall cancer	Qb_{AC} [counts/min/day] Heidelberg (cases n=1,069)			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Cases n=	295	296	279	199
Model 1	1	0.96(0.82;1.15)	1.08(0.91;1.29)	1.10(0.90;1.35)
Model 2	1	0.98(0.83;1.15)	1.09(0.91;1.30)	1.11(0.89;1.37)
Model 3	1	0.93(0.78;1.12)	1.00(0.81;1.25)	0.96(0.72;1.29)
	Potsdam (cases n=1,121)			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Cases n=	534	316	163	108
Model 1	1	0.99(0.85;1.15)	0.93(0.75;1.15)	1.09(0.81;1.47)
Model 2	1	0.97(0.83;1.13)	0.92(0.74;1.15)	1.05(0.77;1.45)
Model 3	1	0.93(0.79;1.10)	0.87(0.68;1.12)	0.96(0.67;1.38)

Model 1 – not adjusted

Model 2 – adjusted for sex and educational attainment (none, primary school completed, technical/professional school, secondary school, longer education) stratified by age

Model 3 – adjusted for sex, BMI (<18.5, ≥18.5<23.0, ≥23.0<25, ≥25.0<30.0, ≥30.0), fruit intake (<50g/day, ≥50<100g/day, ≥100<150g/day ≥150g/day), vegetable intake (<100g/day, ≥100<200g/day, ≥200<300g/day ≥300g/day), red meat intake (<30g/day, ≥30<60g/day, ≥60<90g/day ≥90g/day), alcohol intake (<5g/day, ≥5<10g/day, ≥10<15g/day, ≥15<20g/day ≥20g/day), smoking status (never, former smoker, smoker), hypertension (yes, no), life satisfaction (very satisfied, moderately satisfied, moderately unsatisfied, very unsatisfied), vitamin use (yes/no), mineral use (yes, no), stratified by age

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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 *„Physical activity and chronic disease risk: development and evaluation of a physical activity index and baseline physical activity data calibration in EPIC Germany".* selbstständig angefertigt und verfasst habe und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt wurden. Die geltende Promotionsordnung der Technischen Universität Berlin (Promotionsordnung Dr. P.H. vom 16.03. 1999) ist mir bekannt. Teile der Arbeit sind im Rahmen des Promotionsvorhabens bereits veröffentlicht worden und als solche gekennzeichnet.* Weiterhin versichere ich, die Arbeit an keiner anderen Hochschule oder Fachhochschule eingereicht zu haben.

Unterschrift **Berlin, 21.10.2013**

*Relevante Publikationen (Originalarbeiten):

1. Wientzek A, Vigl M, Steindor K, Brühmann B, Bergmann MM, Harttig U, Katzke V, Kaaks R, Boeing H. The Improved Physical Activity Index for measuring physical activity in EPIC Germany. PLoS One. 2014 Mar 18;9(3).