

Reliability and validity of the Questionnaire on Annual Physical Activity Pattern: A validation study using combined heart rate and accelerometry data as an objective measurement

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Abstract

Introduction Physical activity (PA) is a modifiable lifestyle factor with great public health potential. However, it is still unclear which type, intensity, and temporal pattern of PA is most beneficial. Therefore, a Questionnaire on Annual Physical Activity Pattern (QUAP) for healthy adults was developed; focusing on a detailed assessment of past year PA. The aim was to investigate its test-retest reliability and validity.

Materials and Methods: The self-administered 22-item questionnaire was evaluated in a study embedded into the European Prospective Investigation into Cancer and Nutrition (EPIC) project. Participants included men and women aged 47-82. Reliability was examined in 119 participants by comparing two measurements taken 6-8 weeks apart. Criterion validity was examined in 1109 participants by comparing the physical activity level (PAL) derived from an accelerometry device (Actiheart) to those from the questionnaire.

Results Reliability was acceptable overall with intraclass correlation coefficients ranging from 0.64 to 0.87, with the exception of the domain sedentary behaviour ($r=0.43$). Regarding validity, the Spearman correlation coefficient was 0.33. Slightly higher correlations were found for men ($r_s=0.34$), and participants with a lower BMI ($r_s=0.36$). Bland-Altman plots showed a mean difference of -0.00 (SD=0.22) for total PA.

Conclusions Our findings suggest that the questionnaire has acceptable reliability and validity comparable to other questionnaires. It enables the identification of domain-specific activity patterns and a differentiation between participants with similar energy expenditure but different behaviour. This additional information about distinct activity patterns may finally enable researchers to analyse PA more specifically in terms of health benefits and to provide more detailed public health recommendations.

Keywords Questionnaire, accelerometer, epidemiology, reliability, validity, physical activity

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Introduction

Physical activity (PA) is a modifiable lifestyle factor with great public health potential regarding risk reduction for several chronic diseases [1-6].

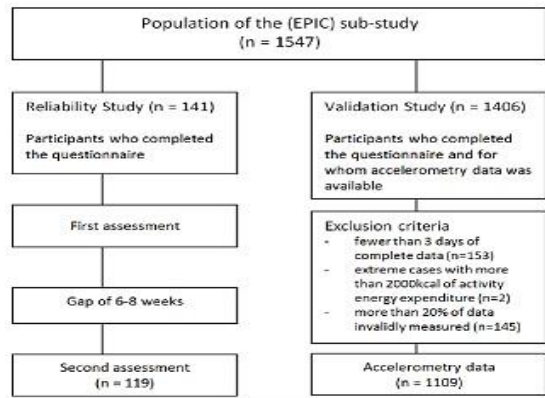


Figure 1: Study design for the Questionnaire on Annual Physical Activity Pattern (QUAP) reliability and validation study

Various guidelines for healthy populations as well as for patients with special diseases or for cancer survivors exist, all recommending to be regularly active and to avoid inactivity. Guidelines for adults (18-64 years old) usually promote about 30 to 60 minutes of moderate to vigorous intensity PA per day on 5 or more days per week. In addition, they recommend participating in muscle-strengthening activities involving major muscle groups on 2 or more days per week [7-9, 6]. However, it is still unclear which type, intensity, and temporal pattern of PA is most beneficial to health [10, 7, 11]. The effect of irregular or acute periods of exhaustive activity may differ from the effect of being constantly active or having an overall active lifestyle. Due to the design of existing questionnaires and the type of information collected, there are still relevant gaps in evidence that hinder formulating more specific public health recommendations.

Due to the advancement in technology, more and more studies use movement sensors such as accelerometers to assess PA [12-20]. This development adds new information to PA and health research. However, such devices also have their limitations. They are, *inter alia*, not able to truly detect contextual information, which includes insight about the type of activity, such as soccer or gymnastics, as well as information about the domain (e.g. occupation, household, leisure time) within which participants engage in a given behaviour [21]. Most of the devices are still not

able to assess certain basic or everyday behaviour, such as walking on an incline, carrying loads, resistance exercise, cycling, upper body movement [22-27, 12, 13], or swimming [16], which can result in an underestimation of energy expenditure (EE).

Thus, applying a combination of both movement sensors and innovative PA questionnaires as complimentary tools is currently considered the most promising approach to assessing PA in epidemiological studies [28, 29].

For our study, we developed an innovative Questionnaire on Annual Physical Activity Pattern (QUAP) for healthy adults. The focus of this new questionnaire is to assess past year PA in all relevant domains and to estimate EE. The questionnaire was recently implemented, complementary to an accelerometry device, in the pretesting of the German National Cohort study, a large-scale, nationwide, prospective follow-up study in Germany that started recruitment in 2014.

The aim of this manuscript is to report on the test-retest reliability and validity studies conducted in the German component of the European Prospective Investigation into Cancer and Nutrition (EPIC). For the latter, physical activity level (PAL) values generated by a heart rate and accelerometer device were compared to those of the QUAP.

Materials and Methods

Questionnaire on Annual Physical Activity Pattern

The self-administered questionnaire consists of 22 items on PA performed over the previous 12 months and is divided into 6 sections to assess the domains occupation, household, locomotion, leisure time PA, sports and exercise, and sedentary behaviour. It covers information about the type of activities as well as the frequency (months/year, days/week or month), duration (hours/day), and perceived intensity of the activity. Levels of intensity are assessed as light, moderate, somewhat heavy, and predominantly

Table 1: Characteristics of the two study populations (reliability n=119; validity n=1109)

	Study population of the reliability study		Study population of the validation study	
	Number	%	Number	%
Total	119	100	1109	100
Sex				
Male	45	37.82	560	50.50
Female	74	62.18	549	49.50
Age (years)				
<55	3	2.52	149	13.44
55-64	23	19.33	419	37.78
65-74	67	56.30	423	38.14
≥75	26	21.85	118	10.64
BMI category (kg/m ²)				
Normal weight (BMI < 25)	34	28.57	350	31.56
Overweight (25 ≤ BMI < 30)	57	47.90	498	44.91
Obese (BMI ≥ 30)	28	23.53	261	23.53

heavy. A list of types of sports is given at the beginning of the section “sports and exercise” as a prompt for participants. As the reference period is a full year, seasonal variations are also considered. The aim is to enable the identification of domain-specific longer-term activity patterns and to differentiate between participants with similar EE but different activity patterns. The latter allows us to differentiate between participants who accumulate the same amount of energy being active but in different domains or through different intensities or frequencies.

Study design and population

The self-administered questionnaire was evaluated in a study embedded into the German component of EPIC. From the original EPIC-cohort in Germany of about 53,000 participants, who were recruited at baseline from 1994 to 1998 [30-32], 1615 participated in the sub-study on extensive phenol typing and were asked to fill out the QUAP. The 1547 participants, who returned the questionnaire, were between 47 and 82 years of age and from the general population of the German cities Potsdam and Heidelberg and their surrounding communities. Ethical approval was obtained from the local ethics boards in Heidelberg and Potsdam prior to recruitment, and informed consent was obtained from all

participants. Recruitment took place at the study centres in Heidelberg and Potsdam, where the participants completed the PA questionnaire and were equipped with a combined heart rate and movement sensor. For calibration of the individual heart rate workload relation, a step test was performed. Exclusion criteria for the long term objective PA measurement were plaster allergy and physical impairment. Additional exclusion criteria for the

step test were severe cardiologic illness, current use of beta blockers (more than half of the maximum dose/day), or a disability that prevented the participant from walking unaided. In case a smaller dose of beta blockers was used by the participant, a shorter version of the step test was performed. For participants, who were excluded from the step test or <4min of step test data were available, age and sex dependent group calibration parameters were applied [33].

Given the results of the validity test and feedback from the study participants, the original questionnaire has been slightly revised. Minor changes in wording were made to clarify the intent of some questions, and a few questions had to be removed due to time restrictions. Results reported from the reliability study refer to the revised version.

Between 2010 and 2013, the questionnaire was completed by a total of 1547 participants (Figure 1). The sub-group for our reliability study consisted of n=141 participants. Questionnaires were mailed to participants twice between March 2012 and February 2013, with an interval of 6-8 weeks between mailings. After the interval, n=119 participants filled out the questionnaire a second time. The completion rate was 84%.

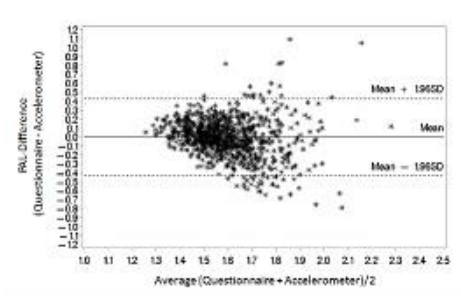


Figure 2: Bland-Altman plot of difference in PAL estimates against the mean of the two measurements: Mean (SD) of the differences: -0.00 (0.22), 95% limits of agreement: -0.43 to 0.43, Mean (SD) of the averages: 1.60 (0.15)

For the validation study a different group of $n=1406$ participants were recruited. Participants were excluded when they had fewer than three days of complete Acti heart data ($n=153$), extreme values of physical activity energy expenditure (PAEE), defined as more than 2000 kcal ($n=2$), or more than 20% of invalid data due to signal noise or missing values ($n=145$). After applying these exclusion criteria, data from $n=1109$ participants were available for analysis (Figure 1).

Heart rate and accelerometer measurement

Objective PA data used for our validity analyses came from a combined accelerometer and heart rate monitoring device (Acti heart, Cambridge Neurotechnology Ltd, Pap worth, UK). The device was attached to the chest via two standard ECG electrodes and measured the participants' heart rate, its variability, and the ECG amplitude. Acceleration was measured by a piezoelectric element with a dynamic range of 1-7Hz (3dB) and a sampling frequency of 32Hz [34]. It showed promising results as a valid tool for the estimation of PAEE over a wide range of activities, including walking and running [35, 36, 34]. A step test was performed to individually calibrate the relationship between heart rate and physical work load. After calibration, participants were instructed to wear the device for 7 consecutive days. Data from at least six full days was available for 95% of the participants. The PAL value for

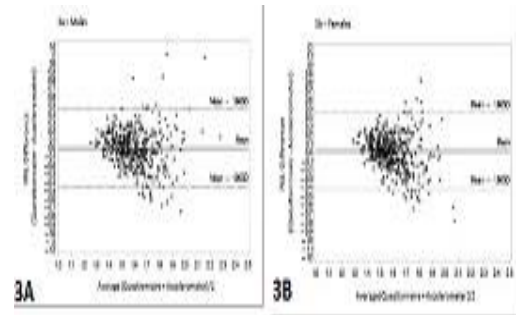


Figure 3a/b: Bland-Altman plot of difference in PAL estimates against the mean of the two measurements, separated by gender: a) Mean (SD) of the differences: -0.01 (0.23), 95% limits of agreement: -0.46 to 0.44, Mean (SD) of the averages: 1.60 (0.15); b) Mean (SD) of the differences: 0.01 (0.22), 95% limits of agreement: -0.42 to 0.44, Mean (SD) of the averages: 1.59 (0.15)

each individual participant was produced from the processed raw acceleration signals by the Acti heart software. Only complete days were used for analyses. A more detailed description of the assessment methods can be found elsewhere [33].

Statistical analyses

The PA outcome measurements used to investigate the reliability and criterion validity of the questionnaire included the number of hours per week spent in each domain (e.g. household, locomotion, or leisure time PA) and the total amount of PA (i.e. the sum of all domains) during the past year. The hours spent per week in each domain were multiplied by the estimated metabolic cost of each activity (metabolic equivalent (MET) value) as determined by the Compendium of Physical Activities [37]. MET values are defined as the ratio of the work metabolic rate to a standard resting metabolic rate of $3.5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ of oxygen uptake. For this reason, one MET is considered to be the energy cost of a person at rest [38, 37]. The total activity, expressed as MET-hours/week, was then converted to a PAL value. It was adjusted to reflect 24 hours by adding missing hours or by subtracting over-reported hours multiplied by 1.3

Table 2: Test-retest reliability of PA* assessed by questionnaire in MET*-hours/week, by domain (n=119)

Physical activity domains	MET-hours/week			
	Mean (SD*)	Mean difference (SD)	Median (IQR*)	Median difference (IQR)
Total PA*				
1 st assessment	170.49 (60.45)	0.34 (46.17)	163.10 (70.43)	2.17 (37.81)
2 nd assessment	175.33 (73.85)		162.00 (79.63)	
Household				
1 st assessment	41.29 (29.24)	1.08 (14.55)	36.90 (41.00)	0.08 (16.60)
2 nd assessment	41.30 (27.86)		36.00 (36.20)	
Locomotion				
1 st assessment	19.72 (18.97)	0.14 (14.25)	14.63 (21.91)	0.00 (10.38)
2 nd assessment	20.45 (22.25)		12.47 (19.56)	
Leisure time walking				
1 st assessment	6.96 (7.93)	0.82 (5.99)	3.75 (8.81)	0.00 (4.03)
2 nd assessment	6.38 (6.71)		4.50 (7.59)	
Leisure time cycling				
1 st assessment	2.90 (4.90)	0.27 (4.38)	0.19 (3.75)	0.00 (0.47)
2 nd assessment	2.80 (5.08)		0.00 (3.38)	
Sports and exercise				
1 st assessment	13.41 (18.96)	-1.77 (20.60)	7.14 (20.00)	0.00 (8.11)
2 nd assessment	14.96 (32.39)		6.00 (19.50)	
Sedentary behaviour				
1 st assessment	63.61 (26.19)	0.61 (28.06)	61.10 (42.25)	0.00 (28.60)
2 nd assessment	62.27 (26.03)		61.10 (35.10)	

* IQR, interquartile range; MET, metabolic equivalent; PA, physical activity; SD, standard deviation.

MET as reported in other studies [39-41]. This MET factor was chosen under the assumption that most of the unreported time was spent with sedentary activities.

Since some of the data distributions were non-normal, non-parametric tests such as the Spearman rank correlation were used to assess reliability and validity. The test-retest reliability of the questionnaire was examined by comparing MET-hours/week of the individual domains and total activity for both of the measurements (6-8 weeks apart). We calculated intraclass correlation coefficients (ICC) and their 95% confidence intervals (CI), using the ICC type '2,1' based on a two-way model of PA scores in participants questioned at two independent, random times. The model considered the time effect on the variability of scores [42].

Criterion validity was examined by comparing the PAL values derived from the questionnaire to those from the objective measurement. The median and interquartile ranges (IQR) of the individual differences between both measurements and the Spearman rank correlations with 95% CIs for the whole group, as well as for subgroups defined by sex, age, and BMI, were calculated. In addition, the agreement between methods was analysed using the Bland-Altman method [43, 44] by plotting the individual PAL differences against the average of the measurements. This enabled the identification of systematic and random errors, outliers, trends, and the extent of agreement. Analyses also included the agreement in individuals, defined as 95% limit of agreement. Limits were defined as mean \pm 1.96 standard deviation (SD) of the differences [39]. Assumptions for this method, i.e. homoscedasticity and normality, were checked.

Table 3: Reliability study: Intraclass correlation coefficient of the questionnaire for total physical activity and for all domains (n=119)

Physical activity assessment comparison	MET-hours/week			
	Intraclass correlation coefficient		95% confidence interval	
	Total Male	Female	Total Male	Female
Total physical activity	0.79 0.71	0.86	0.68, 0.85 0.48, 0.84	0.76, 0.92
Household	0.87 0.78	0.89	0.82, 0.91 0.63, 0.88	0.83, 0.93
Locomotion	0.77 0.86	0.66	0.69, 0.84 0.74, 0.92	0.50, 0.77
Leisure time walking	0.65 0.46	0.70	0.53, 0.74 0.21, 0.67	0.56, 0.80
Leisure time cycling	0.64 0.47	0.75	0.52, 0.73 0.20, 0.67	0.63, 0.84
Sports and exercise	0.70 0.72	0.60	0.59, 0.79 0.54, 0.84	0.41, 0.73
Sedentary behaviour	0.43 0.42	0.43	0.25, 0.58 0.11, 0.65	0.19, 0.61

* MET, metabolic equivalent.

Questionnaires were scanned and verified with Cardiff Teleform V10.7 (available from Digital Documents, Cherry Valley, California) before being transferred into the Statistical Analysis Software (SAS) 9.3 (SAS Institute, Inc., Cary, North Carolina) for analysis.

Results

The 119 participants of the reliability study included more females (n=74) than males (n=45) (Table 1). The total average age was 69.8 years (range 52-80) and did not differ by sex. The group was slightly to moderately overweight with a mean BMI of 26.65 kg/m². A total of 1109 participants took part in the validation study. The population was fairly evenly divided between males (n=560) and females (n=549). Total average age was 64.7 years (range 47-82), which was nearly the same for both sexes. The group was slightly to moderately overweight with a mean BMI of 26.92 kg/m².

Comparing the first and second assessments of the questionnaire for the overall study population in our reliability study, the mean values of the second measurements were slightly lower than the first within all domains, with the exception of sports and exercise (Table 2). The median difference was around zero for each individual domain. For total PA, there was a non-statistically significant median difference (IQR) of 2.17 (37.81) MET-hours/week.

Intraclass correlations ranged from 0.43 to 0.87 (Table 3). The strongest correlations (>0.70) for the total population were observed in the domains household (r=0.87), total PA (r=0.79), and locomotion (r=0.77). Sports and exercise showed a strong correlation (r=0.70), with a slightly broader CI. Leisure time walking and cycling had moderate correlations, and the test-retest correlation of sedentary behaviour was moderate/weak. None of the domains showed weak correlations (<0.29).

Table 4: Validity of total PA* as estimated by questionnaire, compared to objective measurement (n=1109)

Questionnaire compared to heart rate and acceleration device	Physical Activity Level (PAL)		
	Median PAL difference (Quest – Actiheart; IQR**)	Spearman rank correlation coefficient	95% confidence interval
Total population	0.005(0.235)	0.33*	0.27, 0.38
Sex			
Male	-0.011 (0.250)	0.34*	0.26, 0.42
Female	0.011(0.230)	0.31*	0.23, 0.39
Age (years)			
< 65	-0.009 (0.237)	0.29*	0.21, 0.37
≥ 65	0.026 (0.238)	0.26*	0.17, 0.35
BMI (kg/m ²)			
Normal weight (BMI < 25)	-0.009 (0.212)	0.36*	0.26, 0.46
Overweight (BMI ≥ 25)	0.012 (0.256)	0.31*	0.23, 0.38

* $p < 0.0001$; **IQR, interquartile range; PA, physical activity.

Regarding gender-specific correlation coefficients, ICCs for total PA were higher for females ($r=0.86$) than for males ($r=0.71$). Females also had higher correlations than males in the following domains: household, walking, and cycling. Males had higher correlations than females in the domains locomotion and sports and exercise. For the domain sedentary behaviour, similar correlations were observed in both genders.

In our validation study, the median PAL difference between questionnaire and accelerometer for the total population was 0.005 (Table 4). The Spearman correlation coefficient for this comparison was $r_s=0.33$. Slightly higher correlations were found for men ($r_s=0.34$) and participants with a lower BMI ($r_s=0.36$). A lower correlation was found in the group of people over age 65 ($r_s=0.26$).

Bland-Altman plots showed no mean bias between both measurements with a mean difference of -0.00 (SD=0.22) for total PA as well as a mean difference of -0.01 (SD=0.23) for males and 0.01 (SD=0.22) for females (Figure 2 and 3a/b). However, there was slight heteroscedasticity with increasing difference between the accelerometer and questionnaire measures for higher PA levels. The same pattern was seen for both sexes.

While males had more extreme values, values for females showed a better and denser cloud around the mean difference line. The mean average of the PAL values from both instruments was 1.6 in both genders (Figure 3a/b). The plots suggested better agreement between the PAL value of the questionnaire and the Acti heart for less active participants, but larger, yet not systematic, deviations for highly active participants.

Discussion

In this study, test-retest reliability and criterion validity of a self-administered questionnaire assessing past year PA patterns among men and women aged 47-82 years were investigated. Overall, reliability was acceptable, with the exception of the domain sedentary behaviour. Reliability tended to be higher in the domains household, locomotion, and total PA for the entire study population. The correlation of the questionnaire with the heart rate monitoring and accelerometry device regarding PAL was modest. Slightly higher correlations could be seen for males and for participants with a lower BMI. Bland-Altman plots suggested moderate agreement between the PAL value of the questionnaire and the PAL value of the accelerometry device without a mean bias. Slight

heteroscedasticity indicated better agreement for participants with low PA than for highly active participants.

The observed levels of reliability and validity for the past year PA questionnaire were comparable to these instruments assessing habitual or global PA [45-50]. An extensive review by Helmerhorst et al. [51] about existing and more recently developed PA questionnaires with varying timeframes showed that most of the reliability correlation coefficients in our study were in the same range (0.62-0.76). Our reliability results regarding total PA and the domains household and locomotion were even better, with $r=0.79$, 0.87 , and 0.77 , respectively. The domain sedentary behaviour, in contrast, showed a lower reliability with $r=0.43$. Regarding validity, QUAP, with a correlation of $r_s=0.33$, is in the centre of the range (0.25-0.41) observed in the review. It must be taken into consideration, however, that these reference values include a broad range of PA questionnaires with all kinds of timeframes. Additionally, the relatively weak correlation may reflect measurement errors in the accelerometry device as much as in the questionnaire.

A general limitation of this study is that estimating total EE objectively over 7 days is not a true "gold standard" to use as comparison method to assess the validity of the QUAP. Both methods have their limitations, which leads to a lesser degree of agreement between the two. The currently most accurate method of measuring total EE is doubly labelled water (DLW). However, due to its high costs and feasibility aspects, it was not suitable for our large-scale study. Thus, assessing the agreement of the questionnaire with objectively measured data is the most feasible approach to provide valuable insights into the validity of the instrument. The device was worn for only a 1-week period, which is not representative of the total 12 months assessed by our questionnaire. Additionally, the accelerometry device focusses on the assessment of counts and their transformation into energy, whereas our questionnaire focusses on PA in different domains and the resulting EE. The two

instruments are, however, comparable due to the fact that our questionnaire is able to compute a PAL value similar to the PAL value produced by the device. Regarding the age of our study population, we have a relatively old group, with an average age of 65 years. This is caused by the utilisation of our questionnaire within the EPIC project, which started recruitment at baseline between 1994 and 1998. Results show that younger participants (<65 years of age) tend to have a lower median PAL difference, suggesting better agreement, than their older counterparts. It is known that the assessment of PA in older adults is a challenge, partly due to the fact that they are more likely to engage in light to moderate intensity PA, which is the most difficult type of activity to assess [52].

Strengths of our study are the relatively large and well-distributed sample of men and women and the wide age range. The study population was recruited in the EPIC study centres, which ensured a standardised and high-quality assessment. Both recruitment and measurements were performed by trained staff and according to standardised protocols. The main method for the criterion validity, the Acti heart device, provided us with heart rate and activity data over several 24h days. Compared to devices using accelerometry only, the Acti heart uses a combination of heart rate and accelerometry and calculates PA related variables within a branched equation model using parameters individually set for each participant through step test calibration and sleeping heart rate recordings. This results in an improved precision in the estimation of PAEE and PAL [53]. The device is waterproof, which enabled continuous wear, and is considered to be an acceptable method of validating questionnaires. A number of studies that tested heart rate monitors including accelerometry against indirect calorimetry and the doubly labelled water method found good results for the assessment of walking, running, and PAEE [35, 34, 54].

Comparing different types of assessment methods, such as subjective versus objective methods, is additionally advantageous in that

both are supposed to have an individual error structure that is conceptually independent from the other. Therefore, the correlations between the objective measurements and the questionnaire tend to be underestimated [55, 45]. This does not apply to validity studies comparing two PA questionnaires, as questionnaires tend to have a similar error structure.

Our reliability analyses confirmed the frequent finding that sedentary behaviour is difficult to assess with questionnaires. This is a common problem [56-58], as questionnaires are more reliable and valid for activities of moderate-to-vigorous intensity [12]. Assessing PA correctly is a difficult task, as it is multidimensional and complex. Given the derivative characteristics of the different assessment methods, there is no single method suitable for capturing all dimensions and domains of PA and thus covering all its aspects. Questionnaires can provide details and context of behaviour patterns, and they are good at assessing the type of activity and differentiating between domains. Electronic devices, on the other hand, are good at quantifying the amount and intensity of PA and the amount of sedentary behaviour. Large-scale studies should therefore implement both assessment methods. This will enable researchers to use the most appropriate data for their research question.

Conclusions

Our questionnaire aims to assess PA in all relevant domains, to identify domain-specific activity patterns, and to differentiate between participants with similar EE but different activity patterns. More information about distinct activity patterns may finally enable researchers to analyse PA more specifically in terms of health benefits and to provide more detailed public health recommendations. This study has shown that the QUAP questionnaire has acceptable reliability and criterion validity for the measurement of past year PA in a population of healthy men and women. Thus, it appears to be a feasible tool to assess PA in epidemiological studies such as the National Cohort in Germany.

Learning Points

Improved assessment of distinct physical activity patterns may enable more detailed public health recommendations.

The newly developed questionnaire has acceptable reliability and criterion validity for the measurement of past year PA.

The questionnaire appears to be a feasible tool for epidemiological studies to assess PA in all relevant domains.

Abbreviations

EPIC: European Prospective Investigation into Cancer and Nutrition; PAEE: physical activity energy expenditure; CI: confidence interval; EE: energy expenditure; ICC: intraclass correlation coefficient; IQR: interquartile range; MET: metabolic equivalent; PA: physical activity; PAL: physical activity level; QUAP: questionnaire on annual physical activity pattern; SD: standard deviation.

Authors' contributions

BB performed the literature research, collected and analysed the data, scanned and verified questionnaires, and drafted the manuscript. KS, MS and BB developed the questionnaire, contributed to the design of the study, and have been involved in interpreting the data and drafting and revising the manuscript. AW, MV, BT, VK, MB, HB and RK were involved in data collection and data cleaning for the accelerometry and questionnaire data. All authors critically read and gave final approval of the version to be published.

Conflict of interest

The author(s) declare that they have no competing interests

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A copy of the Questionnaire on Annual Physical Activity Pattern can be obtained from Prof. Dr. Karen Steindorf, Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany (e-mail: k.steindorf@dkfz-heidelberg.de).

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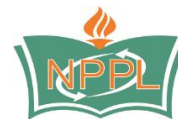
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