Gait & Posture 112 (2024) 22–32

Contents lists available at ScienceDirect

Gait & Posture

journal homepage: www.elsevier.com/locate/gaitpost

Associations of accelerometer-estimated free-living daily activity impact intensities with 10-year probability of osteoporotic fractures in adults

Aleksi Leviäkangas [a], Raija Korpelainen [b,c,d], Pekka Pinola [e,f], Jonathan Fridolfsson [g], Laura Nauha [b,d], Timo Jämsä [a,c], Vahid Farrahi [a,h,*]

[a] Research Unit of Health Sciences and Technology, Faculty of Medicine, University of Oulu, Oulu, Finland
[b] Research Unit of Population Health, Faculty of Medicine, University of Oulu, Oulu, Finland
[c] Medical Research Center, Oulu University Hospital and University of Oulu, Oulu, Finland
[d] Oulu Deaconess Institute Foundation sr., Department of Sports and Exercise Medicine, Finland
[e] Department of Obstetrics and Gynecology, Oulu University Hospital, Wellbeing Services County of North Ostrobothnia, Oulu, Finland
[f] Research Unit of Clinical Medicine, University of Oulu, Oulu, Finland
[g] Center for Health and Performance, Department of Food and Nutrition and Sport Science, University of Gothenburg, Gothenburg, Sweden
[h] Institute for Sport and Sport Science, Division of Data Analytics, TU Dortmund University, Dortmund, Germany

ARTICLE INFO

Keywords:
Osteoporotic fractures
Physical activity
Accelerometry
Bone health
Impact exercise
Movement behavior

ABSTRACT

Purpose: Accelerometers are used to objectively measure physical activity; however, the relationship between accelerometer-based activity parameters and bone health is not well understood. This study examines the association between accelerometer-estimated daily activity impact intensities and future risk estimates of major osteoporotic fractures in a large population-based cohort.

Methods: Participants were 3165 adults 46 years of age from the Northern Finland Birth Cohort 1966 who agreed to wear a hip-worn accelerometer during all waking hours for 14 consecutive days. Raw accelerometer data were converted to resultant acceleration. Impact magnitude peaks were extracted and divided into 32 intensity bands, and the osteogenic index (OI) was calculated to assess the osteogenic effectiveness of various activities. Additionally, the impact peaks were categorized into three separate impact intensity categories (low, medium, and high). The 10-year probabilities of hip and all major osteoporotic fractures were estimated with FRAX-tool using clinical and questionnaire data in combination with body mass index collected at the age of 46 years. The associations of daily activity impact intensities with 10-year fracture probabilities were examined using three statistical approaches: multiple linear regression, partial correlation, and partial least squares (PLS) regression.

Results: On average, participants' various levels of impact were 8331 (SD = 3478) low; 2032 (1248) medium; and 1295 (1468) high impacts per day. All three statistical approaches found a significant positive association between the daily number of low-intensity impacts and 10-year probability of hip and all major osteoporotic fractures. In contrast, increased number of moderate to very high daily activity impacts was associated with a lower probability of future osteoporotic fractures. A higher OI was also associated with a lower probability of future major osteoporotic fractures.

Conclusion: Low-intensity impacts might not be sufficient for reducing fracture risk in middle-aged adults, while high-intensity impacts could be beneficial for preventing major osteoporotic fractures.

1. Introduction

Physical activity is generally considered to have a positive impact on bone health [1,2]. Studies have demonstrated that high-impact exercise is osteogenic, and even a small number of high-impact activities may be sufficient for improving bone density [3,4]. Everyday activity includes various movement and non-movement behaviors, from sedentary activities to stepping and high-intensity exercise [5,6]. Free-living daily activity impact intensities, especially those related to lifestyle, have also been demonstrated to be beneficial for bone health. For example, previous studies have shown daily activity impact intensity in a sample of older adults to be associated with multiple indicators of bone health,

* Corresponding author at: Institute for Sport and Sport Science, Otto-Hahn-Straße 3, Dortmund 44227, Germany.
E-mail address: Vahid.Farrahi@tu-dortmund.de (V. Farrahi).

https://doi.org/10.1016/j.gaitpost.2024.05.002
Received 9 November 2023; Received in revised form 21 March 2024; Accepted 2 May 2024
Available online 5 May 2024

such as bone mineral density (BMD) and the strength strain index (SSI) [7,8]. An osteogenic index has also been presented to assess the osteogenic potential of physical activities [9,10].

In adults, the role of daily activity impact intensities on fracture risk is unclear. To date, several studies have shown that physical activity involving higher intensity impacts is associated with improved bone health indicators and reduced fracture risk [2,7,8,11]. For instance, previous studies have shown that physical activity impact intensities greater than 4.9 g are associated with beneficial changes in proximal femur BMD in premenopausal women [3,4]. However, the effects of low-to-medium impact intensities and their association with bone health and fracture risk are more diverse. In a large cohort study of older adults, an inverse relationship between low-impact intensity physical activity and risk of hip, vertebral, and total fractures was observed [12]. Similarly, increasing leisure time spent in light-intensity activities, such as walking, is protective against hip fractures [13,14]. However, an Australian population-based study, found evidence that adults who walked more were at greater risk for low-trauma fractures than adults who were more sedentary [15]. A recent comparative study and meta-analysis of exercise trials found no clear indication that high-intensity exercise is more beneficial than low-to-moderate intensity exercise for areal BMD at the lumbar spine and hip in adults [16], suggesting that all impact intensities may be related to bone health indicators and fracture risk.

In recent years, the emergence of accelerometers in large-scale epidemiological studies has provided the opportunity to continuously monitor human movement and non-movement behaviors under free-living conditions [17,18]. Accelerometers can provide more precise activity data than self-report questionnaires, providing researchers with access to the entire daily activity behavior continuum [6,19,20]. This allows various daily activity impact intensity bands that represent the full spectrum of impact intensities to be calculated from accelerometer data [3,4,21]. However, neighboring intensity bands are often highly correlated with each other, introducing the problem of multicollinearity into the data. A common approach to dealing with this issue (but not eliminating it) is to classify the accelerometer data into several activity categories, such as sedentary behaviors and light, moderate, and vigorous-intensity physical activity as defined by energy expenditure [6,8,21–25]. Alternatively, a recent consensus statement has suggested using multivariate pattern analysis to counter the known multicollinearity issue [17].

Previous studies with a limited number of participants have examined the associations of accelerometer-estimated physical activity intensities with indicators of bone health in different populations [2–4,7,8,11,21,26,27]. The present population-based study of middle-aged adults examines the relationship between accelerometer-based daily activity impact intensities under free-living conditions and the risk of major osteoporotic fractures. Our aim was to investigate whether and how the accelerometer-measured daily activity impact intensities under free-living conditions is associated with estimated future 10-year-risk of hip fractures and all major osteoporotic fractures.

2. Materials and methods

2.1. Study design and participants

This cross-sectional study used data from the Northern Finland Birth Cohort 1966 study (NFBC1966), originally including participants whose date of birth was expected to be in the year 1966 in northern Finland. A total of 12,056 live-born children were initially involved in the cohort study. Since birth, cohort members have been regularly monitored prospectively, whereby data on their health, lifestyle, and socioeconomic status have been collected. By the latest follow-up in 2012, 10,321 (86 % of all cohort members) individuals with known addresses were still alive, and were reached to participate in the follow-up assessment. This latest follow-up involved completing questionnaires and attending a clinical measurement day. Out of the 10,321 living cohort members with known addresses, 5840 (48 % of all cohort members and 57 % of those who were reached to participate in the latest follow-up) completed the questionnaires and agreed to attend the clinical measurement day. Among these participants, a total of 3165 (54 % of those who agreed to participate in the latest follow-up) individuals provided all the necessary data for the present study. More comprehensive information about the NFBC1966 study objectives, recruitment, and follow-ups can be found elsewhere [28,29].

Study participants from the NFBC1966 who had participated in the latest follow-up at the age of 46 and who had agreed to wear an accelerometer for measurement of waking activities were eligible to participate in the current study. The 46-year follow-up included mail-delivered questionnaires with items about health, medication, health behaviors, and socioeconomic status. Furthermore, participants attended a clinical examination where trained nurses drew fasting blood samples for further analysis.

2.2. Measurements

2.2.1. Accelerometer data processing

Participants (n = 5861) attending the clinical examination were asked to wear a hip-worn tri-axial accelerometer (Hookie AM20; Traxmeet Ltd., Espoo, Finland) for 14 consecutive days during all waking hours except during water-based activities. Raw acceleration signals were collected and stored at a sampling rate of 100 Hz. The raw data from three axes were transformed into resultant acceleration using the Euclidean norm ($\sqrt{x^2 + y^2 + z^2}$) for all subsequent data processing.

The resultant accelerometer data were segmented into non-overlapping 5 second (sec) epochs, and each segment's mean average deviation (MAD) was calculated [30]. MAD describes the mean distance of data points from the resultant mean [31,32]:

$$MAD = \frac{1}{n} \sum |r_i - \bar{r}|$$

Subsequently, 5 sec MAD values were averaged over the course of 1 minute (min) to obtain non-overlapping 1 min MAD values [30,31]. All intervals with at least 60 consecutive 1 min MAD values below 0.02 g were marked as non-wear time and removed. The remaining 1 min MAD values identified as wear time were then categorized into sedentary (< 0.0167 g), light-intensity physical activity (≥ 0.0167 to < 0.091 g), moderate-intensity physical activity (≥ 0.091–0.414 g), and vigorous-intensity physical activity (≥ 0.414 g). The thresholds for classifying sedentary and physical activity intensities from MAD values have been validated elsewhere [21,24].

To minimize the effects of artifacts induced by the action of removing and attaching the monitor, the first and last two minutes of each interval identified as wear time were removed. Previous studies have implemented a similar approach for data cleaning [30,33]. Additionally, the first day that the participants received the monitor was excluded from the analysis to provide comparable results. Participants had to provide at least four valid accelerometer measurement days to meet the inclusion requirement; a valid day was defined as at least 10 h of monitor wear time.

2.2.2. Classification of daily activity impact intensities and the osteogenic index

In all intervals marked as wear time, acceleration peaks (impacts) were detected as the highest point between two adjacent values from the resultant acceleration data. All peaks exceeding an acceleration magnitude of 1.3 g were identified and marked. The detected peaks were then categorized into 32 gradually widening impact intensity bands, as proposed by previous research [3,4,21,30]. The impact intensity bands ranged from 1.3 g to 10.3 g, and all peaks exceeding 10.3 g were assigned to the final band (>10.3 g). The detected peaks were also classified into the following categories: low impact (1.5 g to 2.0 g), medium impact (2.0–2.5 g), and high impact (>2.5 g) [21]. The cumulative count in each intensity band and category was averaged over the valid measurement days to obtain average daily counts.

An osteogenic index (OI) was calculated based on previous studies [9,22] using the 32 impact intensity bands of each measurement day and then averaged across all valid measurement days [31,34]. The OI was calculated according to the following equation:

$$OI = \sum_{j=1}^{32} a_j \ln\left(N_j + 1\right),$$

where a_j denotes the lower limit of the impact intensity band at index j, and N is the count of peaks at band j. The OI was introduced as a metric to assess the osteogenic effectiveness of various activities [8].

2.2.3. 10-year probability of hip and all major osteoporotic fractures

We employed the fracture risk assessment tool (FRAX), which estimates the 10-year probability of hip and all major osteoporotic fractures using clinical risk factors. The FRAX tool has been validated and is among the most accepted tools in clinical practice [35,36]. This tool was developed to assist physicians in diagnostics and preventive care. It estimates the 10-year probability of all major osteoporotic fractures (clinical spine, forearm, hip, and humerus), and a separate estimate of the 10-year probability of a hip fracture. The FRAX models use clinical risk factors, which were originally developed using population-based cohorts from different continents [37]. The risk factors used for calculating FRAX include age, sex, BMI, previous fractures, hip fractures of mother and father, smoking, alcohol use, use of glucocorticoids, rheumatoid arthritis, and diseases associated with osteoporosis (Table 1).

BMD was not measured in the 46-year follow-up. Therefore, we used relevant charts for Finland to estimate 10-year probability of hip and all major osteoporotic fractures for both sexes without BMD (https://www.sheffield.ac.uk/FRAX/charts.aspx).

2.2.4. Self-reported data

The participants' sex was extracted from their medical records. Participants self-reported their previous history of fractures, parental hip fractures, and whether they had rheumatoid arthritis. They also provided information on their medication use and whether they had type I diabetes or premature/early menopause. Several questions about drinking and smoking were used to determine each participant's smoking status (non-smoker, former smoker, current smoker) and daily alcohol consumption. Participants were considered at risk for alcohol use if they consumed three or more units of alcohol per day as specified in the FRAX tool's instructions. In Finland, a unit of alcohol is defined as 12 g of pure alcohol.

Table 1
Risk factors for estimating 10-year probability of hip and all major osteoporotic fractures. The FRAX tool provides fracture probabilities based on the number of risk factors present in an individual. These risk factors within the FRAX tool carry varying weights. For instance, smoking and excessive alcohol consumption are considered relatively weak risk factors, whereas a history of previous fracture or a family history of hip fracture are regarded as strong risk factors.

FRAX-tool variables	Description
BMI	The estimates of fracture probabilities are different depending on BMI level.
Sex	The estimates of fracture probabilities are different depending on the gender.
Previous fracture(s)	Having history of previous fracture is a risk factor
Parental hip fracture	Having history of previous parental hip fracture is a risk factor.
Current smoking status	Smoking currently is a risk factor.
Rheumatoid arthritis	Having Rheumatoid arthritis is a risk factor.
Glucocorticoid medication	Oral daily dose of glucocorticoid medication is a risk factor.
Alcohol risk consumption	Excessive alcohol consumption is a risk factor. 3 or more units / day ($\geq$ 36 g of pure alcohol per day) is considered as high alcohol consumption.
Secondary osteoporosis	Type 1 diabetes, hypogonadism (males), and/or premature menopause (< 45 years) are risk factors.

2.2.5. Clinical examination

Trained nurses measured the height and weight of all participants, from which BMI was calculated. Testosterone and luteinizing hormone (LH) levels were measured from fasting blood samples. They were used to categorize hypogonadism for male participants: as primary hypogonadism (testosterone $<$ 12.1 nmol/l and LH $>$ 9.4 mUI/l), secondary hypogonadism (testosterone $<$ 12.1 nmol/l and LH $<$ 9.4 mUI/l), and compensated hypogonadism (testosterone $>$ 12.1 and LH $>$ 9.4). The thresholds for testosterone and LH were decided by consulting with a physician and considering the relevant literature [38,39].

2.2.6. Confounders

Potential confounders were chosen a priori based on previous research on the association between PA and bone health. Age, sex, marital status, household income, education level, employment status, and health-related quality of life score were used as confounders.

In Finland, where data for the present study were collected, there are four seasons based on light and weather conditions: 1) winter-spring transition, 2) spring-summer transition, 3) summer-autumn transition, and 4) autumn-winter transition. Such transitions are likely to influence daily activity behaviors. We carefully examined whether the time of measurement could be a potential confounder in our analysis. We compared the distribution of low, medium, and high daily activity impact intensities across the four seasonal categories in Finland. These results are shown in Supplementary Material, Figure S1. The differences were found to be marginal; therefore, seasonal difference was not considered a potential confounding factor.

2.3. Statistical analysis

Prior to all analyses, the 10-year probabilities of hip and all major osteoporotic fractures were linearly interpolated to transform the discrete estimations into a continuous variable. Participant characteristics were analyzed using standard descriptive statistics. Multicollinearity has been shown to be a major concern when examining the association between physical activity data and different health indicators [17]. Thus, we used several different statistical approaches to examine these associations. To analyze the associations between traditionally categorized impact intensity levels (low, medium, and high), we utilized multiple linear regression analysis, as multicollinearity was minimal (variance inflation factors (VIF) $<$ 5 for low and high categories and <6 for the medium category).

Due to the high collinearity among the variables, the relationship between the 32 intensity bands with osteoporotic fracture probabilities were examined using partial correlation and partial least squares (PLS) regression. Both techniques have been shown to be suitable for examining relationships in the presence of multicollinearity among the independent variables, although for slightly different reasons. Partial correlation coefficients can be interpreted as the *independent* associations of the intensity bands while controlling for the effect of the other bands and confounders and removing the overlapping collinearity between bands [21,30]. PLS, on the other hand, is a data-driven approach that handles the collinearity among explanatory variables using latent variable modelling. This approach breaks the independent variables down into a set of latent variables while maximizing their covariation with the dependent variable [40,41]. Collinearity is approached as a dimensionality reduction problem in which the variance of the explanatory variables shared with the outcome is retained. PLS describes the pattern of associations for the descriptors with the outcome, accounting for the correlated structure of the data. As a result, associations with health are interpreted for each descriptor (each intensity band) considering its *codependency* with the rest, which is different from partial correlation coefficient that shows the independent associations of each intensity band [17]. In the existing literature, partial correlation has been used to assess the independent relationship between daily activity impact intensities and different indicators of bone health [21,30]. Similarly, an increasing number of studies have used PLS regression to assess the relationships between physical activity intensity profiles and various health markers [42–44].

2.3.1. Multiple linear regression

Multiple linear regression models were developed to examine the associations between traditionally categorized impact intensity levels (low, medium, and high) and OI with the 10-year probability of hip and all major osteoporotic fractures. Prior to analysis, the outcome values (i.e., 10-year osteoporotic fracture probabilities) were log-transformed to correct for skewed distribution. The impact categories and OI were standardized, having a mean of zero and standard deviation of one. This standardization was done so that the regression coefficients could indicate the changes in the outcome per one standard deviation (SD) change in the independent variables. Two sets of models were created: unadjusted and adjusted. The unadjusted models included only impact intensity categories (as an independent variable) and a 10-year probability of hip and all major osteoporotic fractures (as a dependent variable). The adjusted model was additionally adjusted for age, sex, marital status, household income, education level, employment status, and health-related quality of life score. VIF were computed to examine whether multicollinearity existed among the independent variables. A VIF value greater than five is typically considered as significant multicollinearity [45].

2.3.2. Partial correlation and partial least squares (PLS) regression

Partial correlation coefficients were calculated between each intensity band and the 10-year probability of hip and all major osteoporotic fractures. The partial correlations were adjusted for the same confounders as the adjusted multiple linear regression models. The 95 % confidence interval (CI) for partial correlation coefficients was calculated with bootstrapping, using 1000 repetitions [46]. Partial correlation coefficients can be interpreted as the independent associations of the intensity bands while controlling for the effect of the other bands and confounders and removing the overlapping collinearity between bands.

We also used PLS regression to examine the association between the 32 impact intensity bands with the 10-year probability of hip and all major osteoporotic fractures. Residualization was performed on the dependent variables to account for sources of variation and confounding [47]. The 10-year probabilities of hip and major osteoporotic fractures were regressed on all covariates (the same ones as in previous steps), and the residual value from each participant was added to the analytical sample mean of predicted values [47]. Prior to PLS regression analysis, daily activity impact intensity profiles and 10-year probabilities of hip and all major osteoporotic fractures were normalized to have a mean value of zero and an SD of 1.

Choosing optimal number of PLS components (latent variables) and model validation was done using Monte Carlo resampling with 1000 iterations and random 4-fold cross-validation [48]. Final decision for component selection was done based on model root mean squared error (RMSE) and the percentage of variance explained by the model in combination with visual inspection.

A single predictive component was subsequently calculated by means of target projection for each validated PLS regression model, making the interpretation simpler. Target projection produces a single vector containing all the predictive variance [49,50] in the impact intensity spectrum related to the 10-year probability of hip and all major osteoporotic fractures. To further evaluate the explanatory power of each variable, selectivity ratios and their CIs were calculated using the target projected component. There has been an increase in the use of selectivity ratios in physical activity research [42–44,46,51]. Selectivity ratios have been shown to perform well when compared to other methods aiming to identify the most influential variables in a PLS model [52,53]. In short, a variable selectivity ratio of 0.50 and a total explained variance of the model (R^2) of 10 % indicates that this particular variable explains 5 % of the total variance in outcome. Subsequently, multivariate correlation coefficients with 95 % CIs were calculated using the selectivity ratios as follows:

$$r = \sqrt{Selectivity\ ratio * explained\ variance\ in\ the\ outcome}$$

The interpretation of multivariate correlation coefficients can be made on the same scale as Pearson's correlation coefficients; however, there is one key difference: the multivariate correlation coefficients should be interpreted as depicting the relative importance of each impact intensity band for the 10-year probability of hip and all major osteoporotic fracture outcomes instead of independent contributions of coefficients from standard regression models [54].

All PLS regression models were validated against random models with permutated data, performing the comparison of the explanatory power of each validated model against randomly constructed models 10,000 times [46]. The proportion of random models that performed better than validated models was reported as the validated models' *p*-values. The CIs were calculated using a jackknife approach, as originally proposed [41]. The PLS regression and partial correlations were performed using MATLAB (R2018a; MathWorks, Inc., Natick, MA); and the multiple linear regression analyses were done with SPSS (Version 25.0; IBM Corporation, Armonk, NY).

3. Results

3.1. Descriptive statistics

Out of the 5861 cohort members who participated in the follow-up study and wore the accelerometer, 4520 (77.1 %) provided valid accelerometer data. Among those with valid accelerometry data, 3187 (54.4 %) provided all the necessary questionnaires and clinical data required for the present study. Of them, 22 participants were excluded from the analysis due to potential confounding effects of underlying medical conditions or specific medication use, resulting in a final sample size of 3165 participants. The characteristics of cohort members participating in the latest follow-up, and those providing valid data for the present study are shown in Supplementary Material, Table S1. Compared with those participating in the follow-up, a similar percentage of participants with valid data were men (44.1 % vs. 42.9 %), married/cohabiting (78.8 % vs. 79.2 %), non-smokers (53.8 % vs. 54.3 %), and with a polytechnic/university degree (25.5 % vs. 31.0 %).

Risk factors used in calculating 10-year probability of osteoporotic fracture and accelerometer-based daily activity intensity in the study sample are shown in Table 2. On average, 71.4 %, 17.4 %, 11.2 % of daily activity intensities were low, medium and high impact, respectively. The average number of valid measurement days was 11.9 (1.8), and the daily accelerometer wear time was 892.2 (70.8) min/d. No participant reported using oral glucocorticoids regularly.

3.2. Multiple linear regression

Table 3 presents the associations of OI and categorized daily activity impact intensities with a 10-year probability of hip and all major osteoporotic fractures. In unadjusted models, a significant positive association was observed between low impacts and the 10-year probability of a hip fracture (β (95 % confidence interval [CI]) = 0.042 (0.003, 0.081); p = 0.035). After adjusting for confounders, a higher number of low-intensity impacts were associated with a greater probability of a 10-year hip and all major osteoporotic fractures (β = 0.085 (0.047,

Table 2
Risk factors used in calculating 10-year probability of osteoporotic fracture and accelerometer-based daily activity intensity in the middle-aged population (n = 3165). The values are means (SD) or counts (%).

	All (n = 3165)	Men (n = 1359)	Women (n = 1806)
Risk factors used in estimating 10-year fracture risk			
Age	46.6 (0.5)	46.6 (0.5)	46.6 (0.5)
BMI	26.5 (4.5)	27.1 (4.0)	26.1 (4.8)
Previous fractures	716 (22.6 %)	429 (31.6 %)	287 (15.9 %)
Parental hip fracture	339 (10.7 %)	116 (8.5 %)	223 (12.3 %)
Smoking status			
Current	555 (17.5 %)	252 (18.5 %)	303 (16.8 %)
Former	890 (28.1 %)	451 (33.2 %)	439 (24.3 %)
Non-smoker	1720 (54.3 %)	656 (48.3 %)	1064 (58.9 %)
Rheumatoid arthritis	30 (0.9 %)	6 (0.4 %)	24 (1.3 %)
Secondary osteoporosis risk factors			
Type 1 diabetes	21 (0.7 %)	14 (1.0 %)	7 (0.4 %)
Male hypogonadism	-	293 (21.6 %)	-
Premature ovarian insufficiency (<45 y)	-	-	202 (11.2 %)
10-year fracture risk			
10-year probability of hip fracture	0.36 (0.31)	0.29 (0.23)	0.42 (0.34)
10-year probability of major osteoporotic fracture	3.17 (1.37)	2.91 (1.27)	3.36 (1.41)
Accelerometer-based metrics			
Valid measurement days	11.9 (1.8)	11.8 (1.9)	11.9 (1.8)
Wear time, min/day	891.9 (71.0)	894.7 (73.5)	889.9 (69.0)
Sedentary, min/day	558.3 (67.8)	560.9 (68.8)	556.3 (66.9)
Light, min/day	266.8 (70.0)	260.6 (71.7)	271.5 (68.2)
Moderate, min/day	63.6 (28.1)	69.9 (30.8)	58.9 (24.8)
Vigorous, min/day	3.2 (6.9)	3.2 (7.2)	3.2 (6.6)
Low impacts, num/day	8331 (3478)	8631 (3510)	8105 (3436)
Medium impacts, num/day	2032 (1248)	2095 (1289)	1985 (1214)
High impacts, num/day	1295 (1468)	1400 (1666)	1217 (1294)
Osteogenic index	361.8 (83.7)	361.0 (88.3)	362.5 (80.2)

0.122); $p < 0.001$ and β = 0.031 (0.009, 0.052); $p = 0.005$, respectively). Similar results were observed for high-impact intensities and the 10-year probability of hip fracture (β = 0.053 (0.009, 0.098); $p = 0.019$) but not for the 10-year probability of all major osteoporotic fractures. However, there was an inverse association between the OI and the 10-year probability of both hip fracture and all major osteoporotic fractures (β = −0.053 (−0.087, −0.020); $p = 0.002$ and β = −0.024 (−0.042, −0.005); $p = 0.015$, respectively). No multicollinearity was detected among the independent predictors (VIF < 5) except for the medium-impact categories, where the VIF was slightly more than five in both unadjusted and adjusted models (VIF = 5.98 and VIF = 6.05, respectively).

3.3. Partial correlation and PLS regression

Partial correlation models showed a similar relationship between a higher count of low impacts and an increased 10-year probability of hip and all major osteoporotic fractures (Fig. 3). For the 10-year probability of all major osteoporotic fractures, impact intensity bands from 1.3 g to 1.9 g had a statistically significant positive correlation. Impact intensity bands ranging from 1.3 g to 4.3 g were positively associated with an increased 10-year probability of hip fractures. The relationships of other impact intensity bands with the 10-year fracture probabilities were not statistically significant. However, the trend of both partial correlation models seemed to indicate some benefit from increasing the amount of very high-intensity impacts regarding the 10-year probability of both fracture types.

The association patterns of the impact intensity spectrum with the 10-year probability of both fracture types is presented in Fig. 4. Overall, the association pattern of both PLS regression models appears to be similar. The main differences are the threshold at which the multivariate correlations change signs and the strength of the associations. For the 10-year probability of hip fracture, the association with impact intensities turned beneficial at approximately 6.4 g, while the strongest correlation among intensity bands was observed at 1.7 g–1.9 g ($r = 0.11$, model R^2 = 0.7 %, and $p = 0.008$, 2 PLS components). The PLS regression model for the 10-year probability of major osteoporotic fractures and impact intensities ($R^2 = 0.3$ %, $p = 0.023$, 1 PLS component) revealed a comparable association pattern—the relationship between daily activity impact intensities and the 10-year probability of major osteoporotic fractures turned beneficial around 5.8 g, and the strongest association was observed at the same 1.7 g – 1.9 g intensity band ($r = 0.05$).

4. Discussion

The present study estimated the impact intensities of daily activities from hip-worn free-living raw accelerometry data in a large population-based sample of middle-aged adults and examined the association of the activity impact intensity with a 10-year probability of hip and all major osteoporotic fractures using three different statistical approaches. On average, 71.4 %, 17.4 %, 11.2 % of daily activity intensities were categorized as low, medium and high impact, respectively. We found that high-impact activities were associated with a reduced estimated 10-year probability of hip and all major osteoporotic fractures, according to

Table 3
Associations of categorized impact intensities with 10-year probability of hip and all major osteoporotic fractures from multiple linear regression analysis.

	10-year probability of all major osteoporotic fractures						10-year probability of hip fracture					
	Unadjusted			Adjusted*			Unadjusted			Adjusted*		
	β (95 % CI)	p	VIF	β (95 % CI)	p	VIF	β (95 % CI)	p	VIF	β (95 % CI)	p	VIF
Low impacts	0.012 (-0.010, 0.033)	0.297	2.84	**0.031 (0.009, 0.052)**	**0.005**	2.91	**0.042 (0.003, 0.081)**	**0.035**	2.84	**0.085 (0.047, 0.122)**	**<0.001**	2.91
Medium impacts	0.002 (-0.029, 0.034	0.890	5.98	-0.013 (-0.044, 0.018)	0.421	6.05	0.0 (-0.057, 0.057)	1.000	5.98	-0.038 (-0.093, 0.016)	0.166	6.05
High impacts	-0.005 (-0.031, 0.021)	0.725	3.98	0.017 (-0.008, 0.042)	0.190	4.05	0.004 (-0.042, 0.051)	0.850	3.98	**0.053 (0.009, 0.098)**	**0.019**	4.05
Osteogenic index	-0.014 (-0.034, 0.005)	0.142	2.22	**-0.024 (-0.042, -0.005)**	**0.015**	2.25	-0.030 (-0.064, 0.005)	0.091	2.22	**-0.053 (-0.087, -0.020)**	**0.002**	2.25

* Adjusted were controlled for age, sex, marital status, household income, education level, employment status and health-related quality of life score. Fracture probabilities were log-transformed prior to analyses. Significant associations are marked in bold.

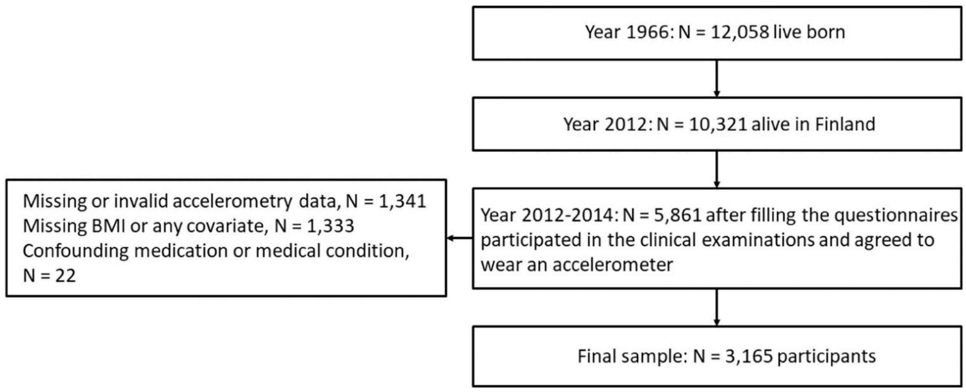

Fig. 1. Participant selection from the NFBC1966.

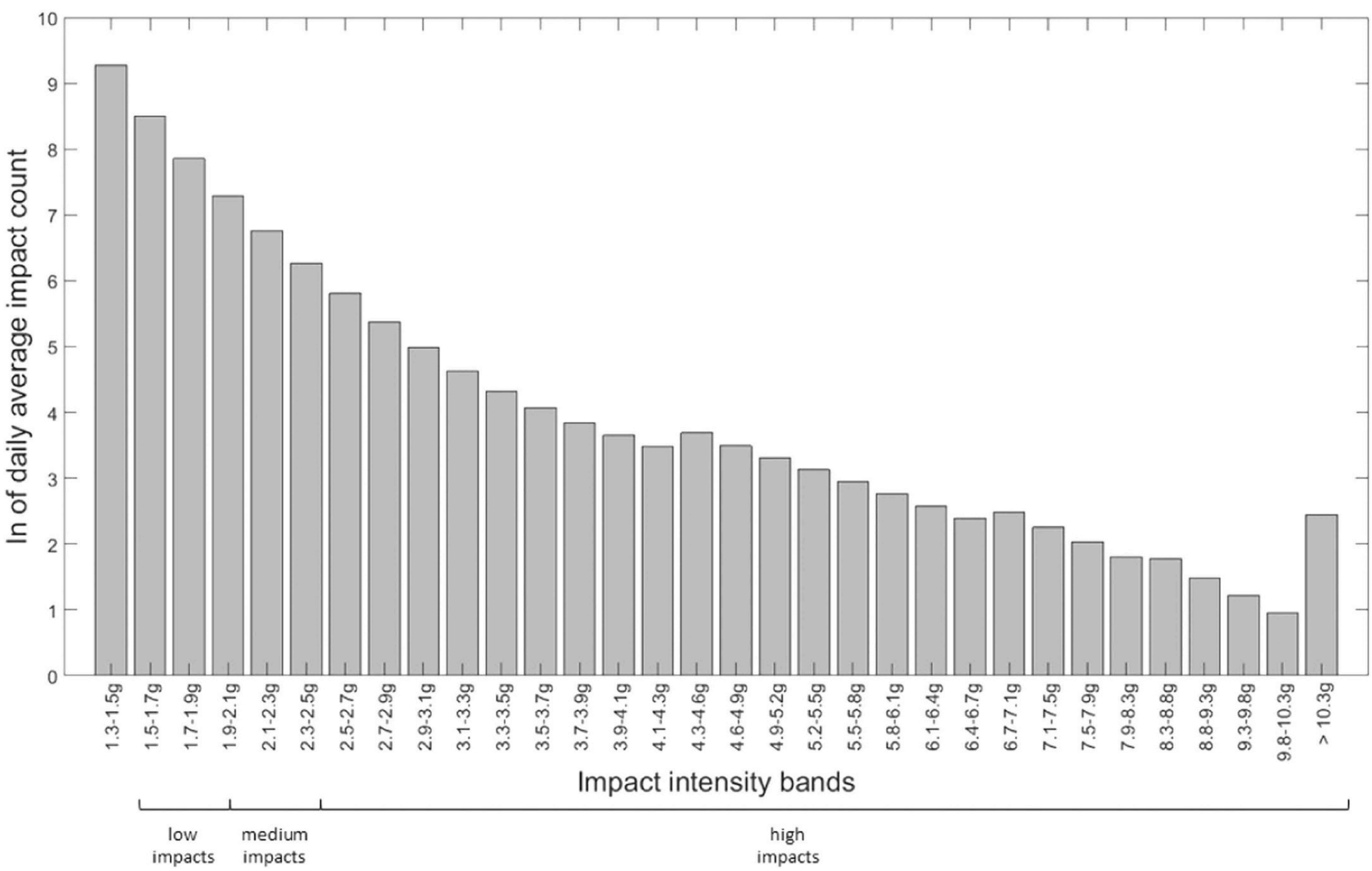

Fig. 2. Study populations' daily activity impact intensity profile presented as log-transformed daily average impact counts at each intensity band. The impact intensity ranges used in traditional 3-class categorization are marked by respective brackets.

multivariate pattern analysis. Higher osteogenic index as a single metric of the osteogenic impact of daily physical activities was also related to a lower 10-year probability for fractures. An increased number of low-intensity impacts was found to be associated with a higher probability of hip and major osteoporotic fractures according to all three statistical approaches.

Our finding of an inverse association between high-level impact intensities and a 10-year probability of hip and all major osteoporotic fractures is consistent with existing literature [2–4,7,8,12]. Previous studies have generally examined the relationships between the self-reported and device-estimated time spent in sedentary behaviors and physical activity intensities with bone health indicators [2–4,7,8,11,21,27,55]. Most existing device-based studies have been performed on a sample of older adults and have had a limited number of participants. Our study measured daily activity using a hip-worn accelerometer. It examined the association of the full spectrum of daily activity impact intensities with a 10-year probability of hip and all major osteoporotic fractures in a large-scale population-based sample of middle-aged adults. In line with existing studies examining the relationship between physical activity and fracture risk [56–61], our findings suggest that physical activity impact intensities are associated with future fracture risk. However, our findings extend the results of previous studies by indicating that accelerometer-estimated medium-to-high-intensity impact activities are associated with a lower estimated 10-year probability of hip and all major osteoporotic fractures.

Using multiple linear regression, we found that a greater amount of

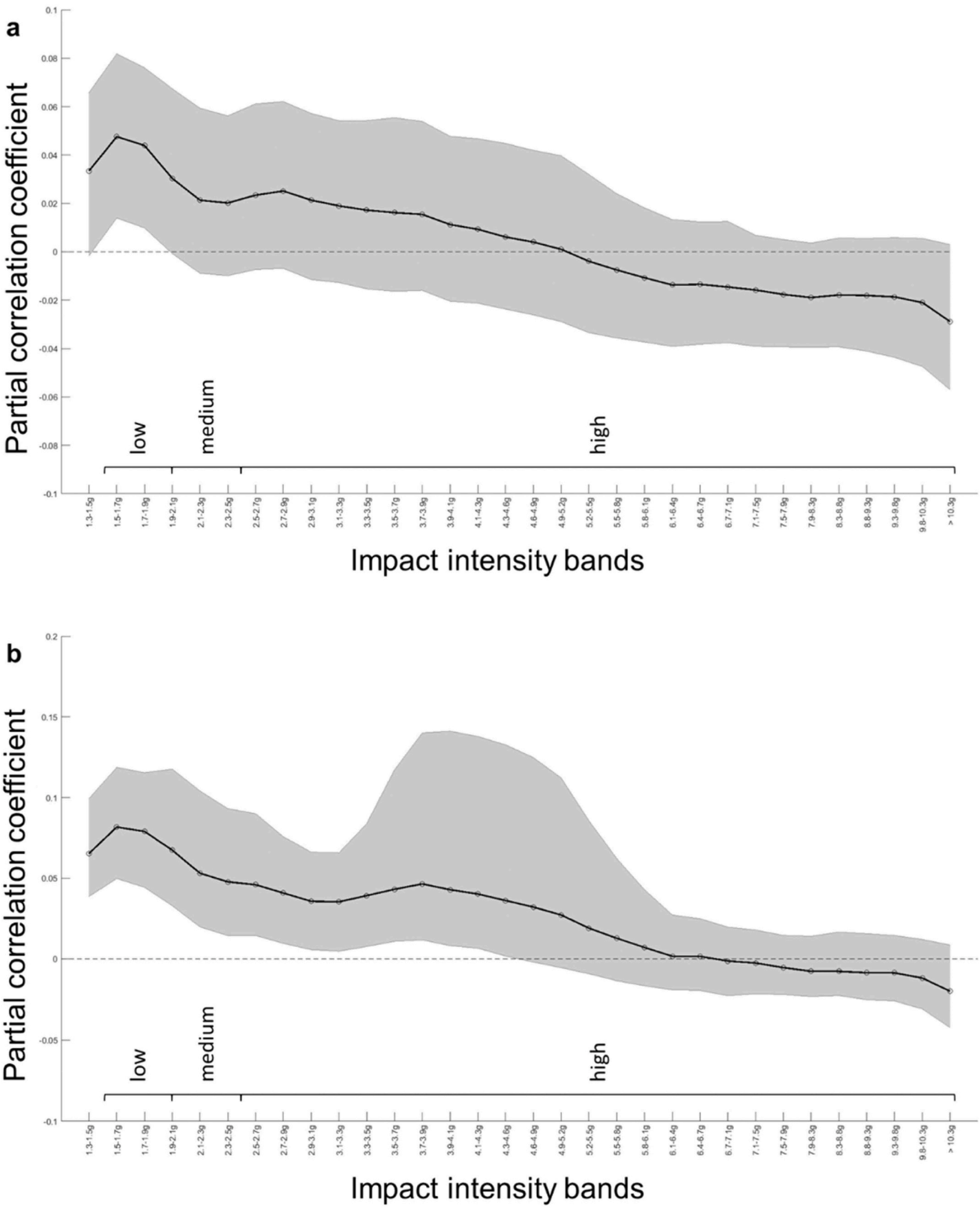

Fig. 3. Association of log-transformed daily impact intensity counts with a) 10-year probability of all major osteoporotic fractures; b) 10-year probability of hip fracture. Associations are presented as partial correlation coefficients with respective 95 % confidence intervals (shaded area). Both models were adjusted for age, sex, marital status, household income, education level, employment status and health-related quality of life score. The impact intensity ranges used in traditional 3-class categorization are marked by respective brackets.

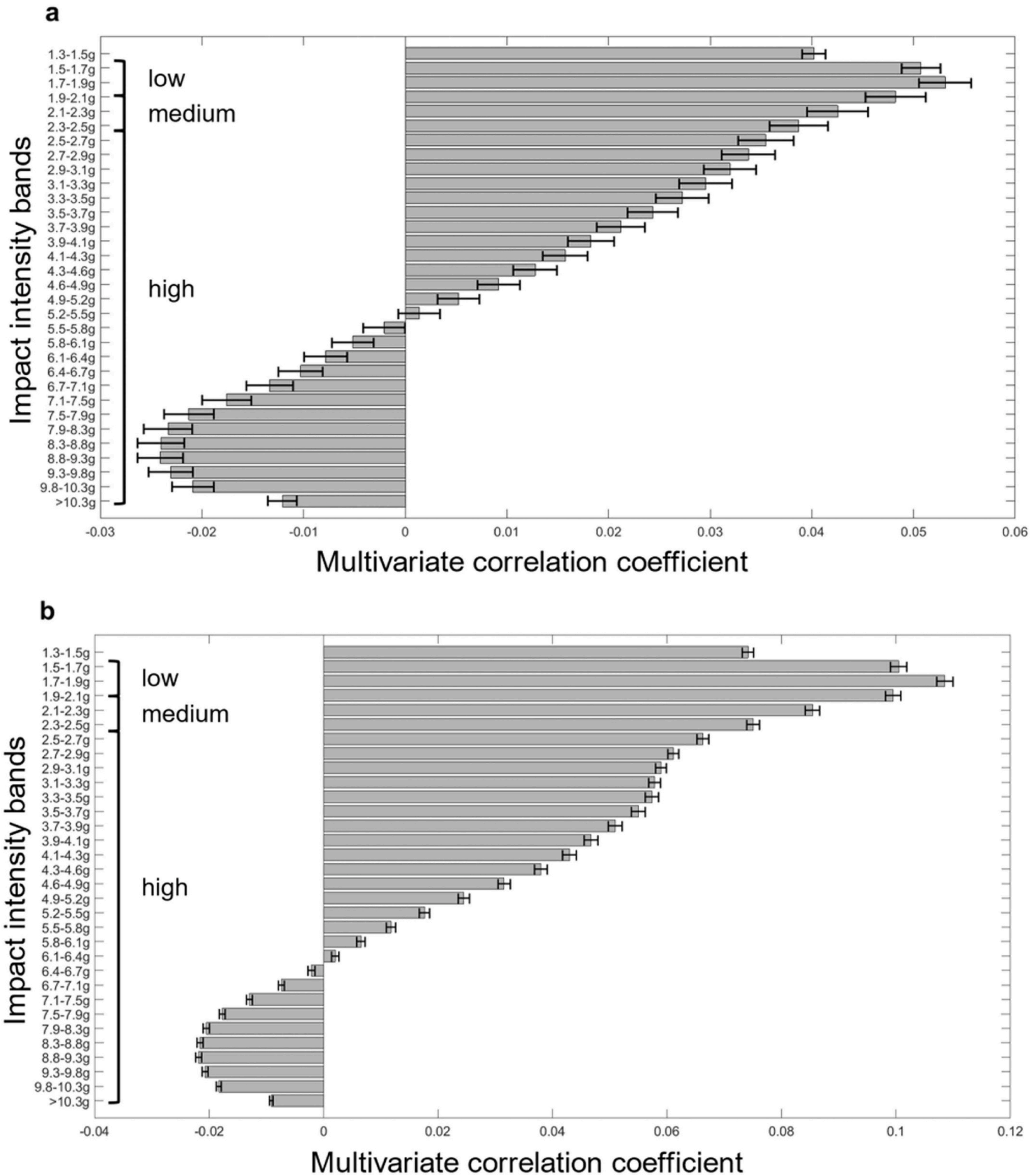

Fig. 4. Association of multivariate daily impact intensity profile with a) 10-year probability of major osteoporotic fracture; b) 10-year probability of hip fracture. Associations are presented as multivariate correlation coefficients with 95 % CIs from the PLS regression models. Both models were adjusted for age, sex, marital status, household income, education level, employment status and health-related quality of life score. A negative bar implies a decrease in the estimated future fracture risk. The impact intensity ranges used in traditional 3-class categorization are marked by respective brackets.

low-intensity (1.5–2.0 g) impacts was associated with a higher 10-year probability of hip and all major osteoporotic fractures. The positive association of low-intensity impacts with a higher future fracture risk was consistent across all three statistical approaches. According to PLS regression and partial correlation models, the strongest positive association of impact intensities with a higher 10-year probability of hip and all major osteoporotic fractures was observed at intensity bands between 1.5–1.9 g. Our study is the first to assess the association of accelerometer-estimated physical activities in more detailed intensity bands in a population-based sample of adults. In line with our findings, a few studies examining the associations of low-intensity impacts have found that an increased number of lower-intensity impacts are associated with a greater risk for fracture or impaired bone health indicators [7,15].

Studies assessing physical activity intensity based on energy expenditure have shown that light-intensity physical activity is associated with reduced fracture risk and improved bone health indicators [12,16,21,26,60]. However, these studies typically include individuals who are older than the participants in the present study. In absolute terms, light-intensity activity in relation to a person's fitness level might be considered moderate intensity. Generally, previous studies have examined the associations of physical activity and fracture risk separately for various intensities, typically accounting for only a partial of impact intensities [7,21]. However, recent studies indicate that human sedentary and activity behaviors represent a continuum [62]. This suggests that activity impact intensities may potentially be interdependent, and codependently related to indicators of bone health.

We used PLS regression due to its capability to deal with the problem of multicollinearity and account for the full spectrum of impact intensities [17]. The results of PLS regression indicate that the effect of impact intensities on future fracture risk turns beneficial with moderate and above-moderate intensities. The threshold at which the association changes signs differs slightly for the 10-year probability of hip and all major osteoporotic fractures (approximately 6.4 g and 5.8 g, respectively). The results from the partial correlation indicate the same pattern but have insignificant associations for high-intensity impacts. This might be partly due to the underlying differences in partial correlation analysis and PLS regression analysis for addressing the problem of multicollinearity (removing the overlapping collinearity among the intensity bands versus addressing the collinearity among the intensity bands). While there are no studies directly examining the association of accelerometer-based impact intensities with fracture risk, Jämsä et al. [3] and Vainionpää et al. [4] have reported positive changes of BMD at the proximal femur with accelerations exceeding 5 g—a threshold rather similar to our findings with PLS regression models.

The strengths of our study include its large population-based sample, a detailed accelerometer-based measurement of activities, and the inclusion of a multivariate pattern analysis method. Compared to previous studies [2,7,8,21,22,26], our study included a longer period of accelerometer-based measurement of activities (i.e., 14 versus seven consecutive days). This likely conferred a more accurate estimation of habitual daily activities and, in turn, more precise estimates of the associations with a 10-year probability of hip and all major osteoporotic fractures.

However, this study also has some limitations. VIF remained less than six in multiple linear regression models. Nonetheless, it has been argued that the thresholds for VIF indicating excess multicollinearity are somewhat arbitrary, and other factors should also be considered [63]. Therefore, we should interpret the results of multiple linear regression models with caution, particularly due to an indication of excess multicollinearity in the medium-impact categories. However, we also examined the associations of impact intensities with PLS regression, which has the ability to address the potential underlying multicollinearities among the independent variables [40,41]. The total variance explained by both PLS regression models was low, but we hypothesize that this is due, at least partly, to the use of BMI-based fracture risk score charts instead of directly measured BMD (which was not available for the current study population). Estimating FRAX with BMD could potentially lead to a more accurate fracture probability estimation [37,64]. The study sample was homogenous in terms of age and ethnicity. Although beneficial with respect to reducing the potential for confounding observed associations, this limits the generalizability of the results to more diverse populations. Additionally, the average age of participants was 46 years, potentially causing a slight overestimation of the fracture probability considering that FRAX models were developed for adults aged 50 years or older. Our study had an observational and cross-sectional design; therefore, inference about the temporality of associations is limited, and causality cannot be determined. The study population was slightly overweight, with an average BMI of 26.5. While the FRAX tool provides varying estimates based on BMI level, future studies should consider the effect of weight on the associations observed between daily impact intensities and fracture risk.

5. Conclusions

This large population-based study among middle-aged adults used three statistical approaches to examine the association of daily free-living activity impact intensities with a 10-year probability of hip and all major osteoporotic fractures estimated with the FRAX tool. High-impact activities were associated with a reduced estimated probability of future hip and all major osteoporotic fractures after accounting for the full impact intensity spectrum. With all three statistical approaches, low-intensity impacts were found to be associated with a higher probability of hip and all major osteoporotic fractures. These findings emphasize the necessity for a high-impact activity to decrease future osteoporotic fracture risk. Future studies could further explore the association pattern of daily activity impact intensities with future fracture risk in different sex-specific age groups.

CRediT authorship contribution statement

Aleksi Leviäkangas: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **Raija Korpelainen:** Project administration, Writing – review & editing. **Pekka Pinola:** Writing – review & editing, Resources. **Jonatan Fridolfsson:** Methodology, Writing – review & editing. **Laura Nauha:** Data curation. **Timo Jämsä:** Supervision, Writing – review & editing. **Vahid Farrahi:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

None to disclose

Acknowledgements

This study has received funding from the Ministry of Education and Culture in Finland [grant numbers OKM/20/626/2022, OKM/76/626/2022, OKM/68/626/2023, OKM/86/626/2014, OKM/43/626/2015, OKM/17/626/2016, OKM 47/626/2017, OKM/78/626/2018, OKM/54/626/2019, OKM/85/626/2019, OKM/88/626/2019, OKM/1096/626/2020]. NFBC1966 received financial support from the University of Oulu Grant no. 24000692, Oulu University Hospital Grant no. 24301140, and ERDF European Regional Development Fund Grant no. 539/2010 A31592. The funders played no role in designing the study, collecting, analyzing, and interpreting the data, or writing the manuscript. We thank all cohort members and researchers who participated in the 46-year study. We acknowledge the NFBC project center for their contribution to managing the NFBC1966 study. The authors declare no conflicts of interest. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.gaitpost.2024.05.002.

References

[1] B.R. Beck, Exercise prescription for osteoporosis: back to basics, Exerc. Sport Sci. Rev. 50 (2022) 57–64, https://doi.org/10.1249/JES.0000000000000281.

[2] A.V. Rowlands, C.L. Edwardson, N.P. Dawkins, B.D. Maylor, K.M. Metcalf, K. F. Janz, Physical activity for bone health: how much and/or how hard? Med. Sci. Sport. Exerc. 52 (2020) 2331–2341, https://doi.org/10.1249/MSS.0000000000002380.

[3] T. Jämsä, A. Vainionpää, R. Korpelainen, E. Vihriälä, J. Leppäluoto, Effect of daily physical activity on proximal femur, Clin. Biomech. 21 (2006) 1–7, https://doi.org/10.1016/j.clinbiomech.2005.10.003.

[4] A. Vainionpää, R. Korpelainen, E. Vihriälä, A. Rinta–Paavola, J. Leppäluoto, T. Jämsä, Intensity of exercise is associated with bone density change in premenopausal women, Osteoporos. Int. 17 (2006) 455–463, https://doi.org/10.1007/s00198-005-0005-x.

[5] V. Farrahi, M. Kangas, R. Walmsley, M. Niemelä, A. Kiviniemi, K. Puukka, P. J. Collings, R. Korpelainen, T. Jämsä, Compositional associations of sleep and activities within the 24-h cycle with cardiometabolic health markers in adults, Med. Sci. Sports Exerc. 53 (2021) 324–332, https://doi.org/10.1249/MSS.0000000000002481.

[6] V. Farrahi, M. Rostami, D. Dumuid, S.F.M. Chastin, M. Niemelä, R. Korpelainen, T. Jämsä, M. Oussalah, Joint profiles of sedentary time and physical activity in adults and their associations with cardiometabolic health, Med. Sci. Sport. Exerc. 54 (2022) 2118–2128, https://doi.org/10.1249/MSS.0000000000003008.

[7] K. Hannam, K.C. Deere, A. Hartley, U.A. Al-Sari, E.M. Clark, W.D. Fraser, J. H. Tobias, Habitual levels of higher, but not medium or low, impact physical activity are positively related to lower limb bone strength in older women: findings from a population-based study using accelerometers to classify impact magnitude, Osteoporos. Int. 28 (2017) 2813–2822, https://doi.org/10.1007/s00198-016-3863-5.

[8] J. Johansson, A. Nordström, P. Nordström, Objectively measured physical activity is associated with parameters of bone in 70-year-old men and women, Bone 81 (2015) 72–79, https://doi.org/10.1016/j.bone.2015.07.001.

[9] R. Ahola, R. Korpelainen, A. Vainionpää, T. Jämsä, Daily impact score in long-term acceleration measurements of exercise, J. Biomech. 43 (2010) 1960–1964, https://doi.org/10.1016/j.jbiomech.2010.03.021.

[10] C.H. Turner, A.G. Robling, Designing exercise regimens to increase bone strength, Exerc. Sport Sci. Rev. 31 (2003) 45–50, https://doi.org/10.1097/00003677-200301000-00009.

[11] C.-A. Ng, L.B. McMillan, B. Beck, L. Humbert, P.R. Ebeling, D. Scott, Associations between physical activity and bone structure in older adults: does the use of self-reported versus objective assessments of physical activity influence the relationship? Osteoporos. Int. 31 (2020) 493–503, https://doi.org/10.1007/s00198-019-05208-y.

[12] M.J. LaMonte, J. Wactawski-Wende, J.C. Larson, X. Mai, J.A. Robbins, M.S. LeBoff, Z. Chen, R.D. Jackson, A.Z. LaCroix, J.K. Ockene, K.M. Hovey, J.A. Cauley, Association of physical activity and fracture risk among postmenopausal women, JAMA Netw. Open 2 (2019) e1914084, https://doi.org/10.1001/jamanetworkopen.2019.14084.

[13] D. Feskanich, A.J. Flint, W.C. Willett, Physical activity and inactivity and risk of hip fractures in men, Am. J. Public Health 104 (2014) e75–e81, https://doi.org/10.2105/AJPH.2013.301667.

[14] D. Feskanich, W. Willett, G. Colditz, Walking and leisure-time activity and risk of hip fracture in postmenopausal women, JAMA 288 (2002) 2300–2306, https://doi.org/10.1001/jama.288.18.2300.

[15] R. Nikander, C. Gagnon, D.W. Dunstan, D.J. Magliano, P.R. Ebeling, Z.X. Lu, P. Z. Zimmet, J.E. Shaw, R.M. Daly, Frequent walking, but not total physical activity, is associated with increased fracture incidence: a 5-year follow-up of an Australian population-based prospective study (AusDiab), J. Bone Miner. Res. 26 (2011) 1638–1647, https://doi.org/10.1002/jbmr.363.

[16] S. Kast, M. Shojaa, M. Kohl, S. von Stengel, M. Gosch, F. Jakob, K. Kerschan-Schindl, B. Kladny, N. Klöckner, U. Lange, S. Middeldorf, S. Peters, D. Schoene, C. Sieber, F. Thomasius, M. Uder, W. Kemmler, Effects of different exercise intensity on bone mineral density in adults: a comparative systematic review and meta-analysis, Osteoporos. Int. 33 (2022) 1643–1657, https://doi.org/10.1007/s00198-022-06329-7.

[17] J.H. Migueles, E. Aadland, L.B. Andersen, J.C. Brønd, S.F. Chastin, B.H. Hansen, K. Konstabel, O.M. Kvalheim, D.E. McGregor, A.V. Rowlands, S. Sabia, V.T. van Hees, R. Walmsley, F.B. Ortega, GRANADA consensus on analytical approaches to assess associations with accelerometer-determined physical behaviours (physical activity, sedentary behaviour and sleep) in epidemiological studies, Br. J. Sports Med. 56 (2022) 376–384, https://doi.org/10.1136/bjsports-2020-103604.

[18] V. Farrahi, M. Niemelä, M. Kangas, R. Korpelainen, T. Jämsä, Calibration and validation of accelerometer-based activity monitors: a systematic review of machine-learning approaches, Gait Posture 68 (2019) 285–299, https://doi.org/10.1016/j.gaitpost.2018.12.003.

[19] J.A. Schrack, R. Cooper, A. Koster, E.J. Shiroma, J.M. Murabito, W.J. Rejeski, L. Ferrucci, T.B. Harris, Assessing daily physical activity in older adults: unraveling the complexity of monitors, measures, and methods, J. Gerontol. Ser. A Biol. Sci. Med. Sci. 71 (2016) 1039–1048, https://doi.org/10.1093/gerona/glw026.

[20] M. Niemelä, M. Kangas, V. Farrahi, A. Kiviniemi, A.-M. Leinonen, R. Ahola, K. Puukka, J. Auvinen, R. Korpelainen, T. Jämsä, Intensity and temporal patterns of physical activity and cardiovascular disease risk in midlife, Prev. Med. (Balt.). 124 (2019) 33–41, https://doi.org/10.1016/j.ypmed.2019.04.023.

[21] T. Savikangas, S. Sipilä, T. Rantalainen, Associations of physical activity intensities, impact intensities and osteogenic index with proximal femur bone traits among sedentary older adults, Bone 143 (2021) 115704, https://doi.org/10.1016/j.bone.2020.115704.

[22] D.L. Belavy, M. Quittner, N.D. Ridgers, Y. Ling, D. Connell, G. Trudel, T. Rantalainen, Beneficial intervertebral disc and muscle adaptations in high-volume road cyclists, Med. Sci. Sports Exerc. 51 (2019) 211–217, https://doi.org/10.1249/MSS.0000000000001770.

[23] J. Chong, P. Tjurin, M. Niemelä, T. Jämsä, V. Farrahi, Machine-learning models for activity class prediction: a comparative study of feature selection and classification algorithms, Gait Posture 89 (2021) 45–53, https://doi.org/10.1016/j.gaitpost.2021.06.017.

[24] V. Farrahi, M. Niemelä, P. Tjurin, M. Kangas, R. Korpelainen, T. Jämsä, Evaluating and enhancing the generalization performance of machine learning models for physical activity intensity prediction from raw acceleration data, IEEE J. Biomed. Heal. Inform. 24 (2020) 27–38, https://doi.org/10.1109/JBHI.2019.2917565.

[25] V. Farrahi, M. Kangas, A. Kiviniemi, K. Puukka, R. Korpelainen, T. Jämsä, Accumulation patterns of sedentary time and breaks and their association with cardiometabolic health markers in adults, Scand. J. Med. Sci. Sports 31 (2021) 1489–1507, https://doi.org/10.1111/sms.13958.

[26] S.F.M. Chastin, O. Mandrichenko, J.L. Helbostadt, D.A. Skelton, Associations between objectively-measured sedentary behaviour and physical activity with bone mineral density in adults and older adults, the NHANES study, Bone 64 (2014) 254–262, https://doi.org/10.1016/j.bone.2014.04.009.

[27] A. Gába, O. Kapuš, J. Pelclová, J. Riegerová, The relationship between accelerometer-determined physical activity (PA) and body composition and bone mineral density (BMD) in postmenopausal women, Arch. Gerontol. Geriatr. 54 (2012) e315–e321, https://doi.org/10.1016/j.archger.2012.02.001.

[28] T. Nordström, J. Miettunen, J. Auvinen, L. Ala-Mursula, S. Keinänen-Kiukaanniemi, J. Veijola, M.-R. Järvelin, S. Sebert, M. Männikkö, Cohort Profile: 46 years of follow-up of the Northern Finland Birth Cohort 1966 (NFBC1966), Int. J. Epidemiol. 50 (2021) 1786–1787.

[29] V. Farrahi, M. Niemelä, M. Kärmeniemi, S. Puhakka, M. Kangas, R. Korpelainen, T. Jämsä, Correlates of physical activity behavior in adults: a data mining approach, Int. J. Behav. Nutr. Phys. Act. 17 (2020) 94, https://doi.org/10.1186/s12966-020-00996-7.

[30] T. Savikangas, A. Tirkkonen, M. Alen, T. Rantanen, R.A. Fielding, T. Rantalainen, S. Sipilä, Associations of physical activity in detailed intensity ranges with body composition and physical function. a cross-sectional study among sedentary older adults, Eur. Rev. Aging Phys. Act. 17 (2020) 4, https://doi.org/10.1186/s11556-020-0237-y.

[31] H. Vähä-Ypyä, T. Vasankari, P. Husu, J. Suni, H. Sievänen, A universal, accurate intensity-based classification of different physical activities using raw data of accelerometer, Clin. Physiol. Funct. Imaging 35 (2015) 64–70.

[32] M. Aittasalo, H. Vähä-Ypyä, T. Vasankari, P. Husu, A.-M. Jussila, H. Sievänen, Mean amplitude deviation calculated from raw acceleration data: a novel method for classifying the intensity of adolescents' physical activity irrespective of accelerometer brand, BMC Sports Sci. Med. Rehabil. 7 (2015), https://doi.org/10.1186/s13102-015-0010-0.

[33] K.C. Deere, K. Hannam, J. Coulson, A. Ireland, J.S. McPhee, C. Moss, M. H. Edwards, E. Dennison, C. Cooper, A. Sayers, M. Lipperts, B. Grimm, J.H. Tobias, Quantifying habitual levels of physical activity according to impact in older people: accelerometry protocol for the VIBE study, J. Aging Phys. Act. 24 (2016) 290–295, https://doi.org/10.1123/japa.2015-0066.

[34] H. Vähä-Ypyä, T. Vasankari, P. Husu, A. Mänttäri, T. Vuorimaa, J. Suni, H. Sievänen, Validation of cut-points for evaluating the intensity of physical activity with accelerometry-based mean amplitude deviation (MAD), PLoS One 10 (2015) e0134813, https://doi.org/10.1371/journal.pone.0134813.

[35] N. Dagan, C. Cohen-Stavi, M. Leventer-Roberts, R.D. Balicer, External validation and comparison of three prediction tools for risk of osteoporotic fractures using data from population based electronic health records: retrospective cohort study, BMJ 356 (2017) i6755, https://doi.org/10.1136/bmj.i6755.

[36] I. Goldshtein, Y. Gerber, S. Ish-Shalom, M. Leshno, Fracture risk assessment with FRAX using real-world data in a population-based cohort from Israel, Am. J. Epidemiol. 187 (2018) 94–102, https://doi.org/10.1093/aje/kwx128.

[37] C. De Laet, J.A. Kanis, A. Odén, H. Johanson, O. Johnell, P. Delmas, J.A. Eisman, H. Kroger, S. Fujiwara, P. Garnero, E.V. McCloskey, D. Mellstrom, L.J. Melton, P. J. Meunier, H.A.P. Pols, J. Reeve, A. Silman, A. Tenenhouse, Body mass index as a predictor of fracture risk: a meta-analysis, Osteoporos. Int. 16 (2005) 1330–1338, https://doi.org/10.1007/s00198-005-1863-y.

[38] E. Ventimiglia, S. Ippolito, P. Capogrosso, F. Pederzoli, W. Cazzaniga, L. Boeri, I. Cavarretta, M. Alfano, P. Viganò, F. Montorsi, A. Salonia, Primary, secondary and compensated hypogonadism: a novel risk stratification for infertile men, Andrology 5 (2017) 505–510, https://doi.org/10.1111/andr.12335.

[39] A. Salonia, C. Bettocchi, J. Carvalho, G. Corona, T.H. Jones, A. Kadioglu, J. I. Martínez Salamanca, S. Minhas, E.C. Serefoglu, P. Verze, EAU guidelines on sexual and reproductive health, Eur. Assoc. Urol. (2022) 232.

[40] S. Wold, M. Sjöström, L. Eriksson, PLS-regression: a basic tool of chemometrics, Chemom. Intell. Lab. Syst. 58 (2001) 109–130, https://doi.org/10.1016/S0169-7439(01)00155-1.

[41] S. Wold, A. Ruhe, H. Wold, W.J. Dunn III, The Collinearity problem in linear regression. The partial least squares (PLS) approach to generalized inverses, SIAM J. Sci. Stat. Comput. 5 (1984) 735–743, https://doi.org/10.1137/0905052.

[42] E. Aadland, O.M. Kvalheim, S.A. Anderssen, G.K. Resaland, L.B. Andersen, Multicollinear physical activity accelerometry data and associations to cardiometabolic health: challenges, pitfalls, and potential solutions, Int. J. Behav. Nutr. Phys. Act. 16 (2019) 74, https://doi.org/10.1186/s12966-019-0836-z.

[43] E. Aadland, O.M. Kvalheim, B.H. Hansen, S. Kriemler, M. Ried-Larsen, N. Wedderkopp, L.B. Sardinha, N.C. Møller, P.C. Hallal, S.A. Anderssen, K. Northstone, L.B. Andersen, International Children's Accelerometry Database (ICAD) Collaborators, the multivariate physical activity signature associated with metabolic health in children and youth: An International Children's Accelerometry Database (ICAD) analysis, Prev. Med. (Balt.) 141 (2020) 106266, https://doi.org/10.1016/j.ypmed.2020.106266.

[44] P.C. Dempsey, E. Aadland, T. Strain, O.M. Kvalheim, K. Westgate, T. Lindsay, K.-T. Khaw, N.J. Wareham, S. Brage, K. Wijndaele, Physical activity intensity profiles associated with cardiometabolic risk in middle-aged to older men and women, Prev. Med. (Balt.) 156 (2022) 106977, https://doi.org/10.1016/j.ypmed.2022.106977.

[45] K. P. Vatcheva, M. Lee, Multicollinearity in regression analyses conducted in epidemiologic studies, Epidemiol. Open Access 06 (2016) 1–20, https://doi.org/10.4172/2161-1165.1000227.

[46] J. Fridolfsson, D. Arvidsson, L.B. Andersen, O. Thorsson, P. Wollmer, B. Rosengren, M.K. Karlsson, M. Dencker, Physical activity spectrum discriminant analysis—a method to compare detailed patterns between groups, Scand. J. Med. Sci. Sports 31 (2021) 2333–2342, https://doi.org/10.1111/sms.14052.

[47] W. Willett, M.J. Stampfer, Total energy intake: implications for epidemiologic analyses, Am. J. Epidemiol. 124 (1986) 17–27, https://doi.org/10.1093/oxfordjournals.aje.a114366.

[48] O.M. Kvalheim, R. Arneberg, B. Grung, T. Rajalahti, Determination of optimum number of components in partial least squares regression from distributions of the root-mean-squared error obtained by Monte Carlo resampling, J. Chemom. 32 (2018) e2993, https://doi.org/10.1002/cem.2993.

[49] O.M. Kvalheim, Interpretation of partial least squares regression models by means of target projection and selectivity ratio plots, J. Chemom. 24 (2010) 496–504, https://doi.org/10.1002/cem.1289.

[50] T. Rajalahti, O.M. Kvalheim, Multivariate data analysis in pharmaceutics: a tutorial review, Int. J. Pharm. 417 (2011) 280–290, https://doi.org/10.1016/j.ijpharm.2011.02.019.

[51] E. Aadland, O.K. Holmøy, A.K.O. Nilsen, The multivariate physical activity signature associated with body mass index in young children, Prev. Med. (Balt.) 145 (2021) 106437, https://doi.org/10.1016/j.ypmed.2021.106437.

[52] O.M. Kvalheim, Variable importance: Comparison of selectivity ratio and significance multivariate correlation for interpretation of latent-variable regression models, J. Chemom. 34 (2020) e3211, https://doi.org/10.1002/cem.3211.

[53] T. Mehmood, S. Sæbø, K.H. Liland, Comparison of variable selection methods in partial least squares regression, J. Chemom. 34 (2020) e3226, https://doi.org/10.1002/cem.3226.

[54] E. Aadland, L.B. Andersen, G.K. Resaland, O.M. Kvalheim, Interpretation of multivariate association patterns between multicollinear physical activity accelerometry data and cardiometabolic health in children—a tutorial, Metabolites 9 (2019) 129, https://doi.org/10.3390/metabo9070129.

[55] C. Ng, D. Scott, M.J. Seibel, R.G. Cumming, V. Naganathan, F.M. Blyth, D.G. Le Couteur, L.M. Waite, D.J. Handelsman, V. Hirani, Higher-impact physical activity is associated with maintenance of bone mineral density but not reduced incident falls or fractures in older men: the concord health and aging in men project, J. Bone Miner. Res. 36 (2021) 662–672, https://doi.org/10.1002/jbmr.4228.

[56] B. Morseth, L.A. Ahmed, Å. Bjørnerem, N. Emaus, B.K. Jacobsen, R. Joakimsen, J. Størmer, T. Wilsgaard, L. Jørgensen, Leisure time physical activity and risk of non-vertebral fracture in men and women aged 55 years and older: the Tromsø Study, Eur. J. Epidemiol. 27 (2012) 463–471, https://doi.org/10.1007/s10654-012-9665-y.

[57] U.M. Kujala, J. Kaprio, P. Kannus, S. Sarna, M. Koskenvuo, Physical activity and osteoporotic hip fracture risk in men, Arch. Intern. Med. 160 (2000) 705–708, https://doi.org/10.1001/archinte.160.5.705.

[58] X. Qu, X. Zhang, Z. Zhai, H. Li, X. Liu, H. Li, G. Liu, Z. Zhu, Y. Hao, K. Dai, Association between physical activity and risk of fracture, J. Bone Miner. Res. 29 (2014) 202–211, https://doi.org/10.1002/jbmr.2019.

[59] S. Han, H.-D. Jang, S. Choi, G.D. Kim, K. Han, H. Lim, B. Koo, K.D. Min, J.-Y. Hong, Changes in physical activity and risk of fracture: a Korean nationwide population-based cohort study, Sci. Rep. 10 (2020) 16266, https://doi.org/10.1038/s41598-020-73495-1.

[60] U. Englund, P. Nordström, J. Nilsson, G. Bucht, U. Björnstig, G. Hallmans, O. Svensson, U. Pettersson, Physical activity in middle-aged women and hip fracture risk: the UFO study, Osteoporos. Int. 22 (2011) 499–505, https://doi.org/10.1007/s00198-010-1234-1.

[61] S. Høidrup, T.I.A. Sørensen, U. Strøger, J.B. Lauritzen, M. Schroll, M. Grønbæk, Leisure-time physical activity levels and changes in relation to risk of hip fracture in men and women, Am. J. Epidemiol. 154 (2001) 60–68, https://doi.org/10.1093/aje/154.1.60.

[62] M.E. Rosenberger, J.E. Fulton, M.P. Buman, R.P. Troiano, M.A. Grandner, D. M. Buchner, W.L. Haskell, The 24-hour activity cycle: a new paradigm for physical activity, Med. Sci. Sports Exerc. 51 (2019) 454–464, https://doi.org/10.1249/MSS.0000000000001811.

[63] R.M. O'brien, A caution regarding rules of thumb for variance inflation factors, Qual. Quant. 41 (2007) 673–690, https://doi.org/10.1007/s11135-006-9018-6.

[64] J.A. Kanis, E. McCloskey, H. Johansson, A. Oden, W.D. Leslie, FRAX® with and without bone mineral density, Calcif. Tissue Int. 90 (2012) 1–13, https://doi.org/10.1007/s00223-011-9544-7.