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Original article

Calcaneal broadband ultrasound attenuation predicts physical capability: EPIC-Norfolk prospective population-based study

Sarah L. Perrott [a,*], Kathryn Martin [b,c], Victoria L. Keevil [d], Nicholas J. Wareham [e], Kay-Tee Khaw [d], Phyo Kyaw Myint [a]

[a] Ageing Clinical & Experimental Research (ACER) Team, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK
[b] Academic Primary Care, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, UK
[c] The Aberdeen Centre for Arthritis and Musculoskeletal Health, University of Aberdeen, Aberdeen, UK
[d] Department of Medicine, University of Cambridge, UK
[e] MRC Epidemiology Unit, Cambridge, UK

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ABSTRACT

Background: Calcaneal ultrasound (broadband ultrasound attenuation – BUA), a marker of bone strength, may predict future physical capability and thus provide a strategy to identify individuals at risk of age-related deterioration of health. This study aims to determine if BUA can predict future physical capability among middle-aged and older adults.

Methods: Summary performance scores (SPS), an objective quantification of physical capability, were devised using participants' measures of standing balance, gait speed and timed chair rises. Associations between BUA and SPS, measured at least six years apart, were investigated using univariable and multivariate sex-specific linear and logistic regression, adjusting for confounders.

Results: 5893 participants were included. In men and women, for every five points lower BUA, there was a 0.2-point decrease in SPS. In women, BUA less than one standard deviation below the mean was associated with low physical capability (defined as SPS 3–6); fully adjusted odds ratio (OR) (95 % confidence interval (CI)) 1.35 (1.01–1.84). No association existed among men; OR (95 % CI) 0.84 (0.59–1.19). Significant risk factors for low physical capability in men with baseline low BUA were: older age [OR 5.77]; high BMI [OR 2.85]; lower social class [OR 1.59]; low physical activity [OR 1.64]. Risk factors among women were: older age [OR 5.54]; high BMI [OR 2.08]; lower education [OR 1.42], low physical activity [OR 1.27]; steroid use [OR 2.05]; and stroke [OR 2.74].

Conclusion: BUA may predict future physical capability in older adults. With further validation, BUA could stratify individuals at risk of deterioration in physical health.

1. Introduction

The global population aged over 65 years is predicted to double by 2050 [1]. At this time, the estimated global life expectancy will be 76 years; in 1950 it was 48 years [2]. Longer life expectancy means a significant proportion of society will experience age-related deterioration in health and frailty, negatively impacting on already overstretched health systems and national economies [2,3]. From a public health perspective, strategies to promote healthy ageing, maintain independence and delay onset of frailty is vital as population demographics continue to shift [4].

Physical capability, a term encompassing a person's ability to perform everyday physical tasks, can be objectively evaluated using tests of gait speed, standing balance and timed chair rises [5]. These highly discriminative physical performance tests are useful markers and predictors of current and future health in older adults [4], with lower physical capability associated with higher risk of disability [6], falls [7], fracture [8] and all-cause mortality [5,9]. Previously, physical

Abbreviations: BUA, broadband ultrasound attenuation;; SPS, summary performance score; 2HC, second health check; BMI, body mass index; SD, standard deviation; OR, odds ratio; CI, confidence interval; ADL, activity of daily living; EPIC, European Prospective Investigation into Cancer; CUBA, calcaneal ultrasound broadband attenuation; DEXA, dual energy X-ray absorptiometry; TDI, Townsend Deprivation Index; HRT, hormone replacement therapy.

* Corresponding author at: Room 4: 013, Polwarth Building, School of Medicine and Dentistry, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, UK.
E-mail address: sarahperrott@doctors.org.uk (S.L. Perrott).

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performance and muscle measures have been used to predict future activities of daily living (ADL) dependence in older adults [10], and thus have been proposed as screening tools for sarcopenia [4,11], frailty [12,13], and 'cognitive frailty' – a precursor of dementia [14].

Calcaneal ultrasound, specifically broadband ultrasound attenuation (BUA), a validated tool used to evaluate bone strength and screen for osteoporosis [15–17], has previously been associated with frailty in older men [18]. Furthermore, poor bone strength strongly correlates with future falls and fracture incidence, reduced independence and mortality [19–22]. BUA measurement is inexpensive, quick to perform and accurate [23], potentially providing a sustainable method to stratify individuals at risk of unhealthy ageing and ADL dependence before further decline. Early identification of markers of physical health deterioration will enable commencement of lifestyle and pharmacological interventions to maximise outcomes [24–26], in addition to future planning at an individual or population level.

To our knowledge, BUA has never been used to predict physical capability and has seldom been used outside the realm of bone health. We aim to investigate whether BUA predicts physical capability in middle-aged and older adults.

2. Material and methods

2.1. Population

The population consists of 5893 European Prospective Investigation of Cancer-Norfolk (EPIC-Norfolk) cohort study participants who had their BUA and physical capability evaluated at least six years apart. The participant enrolment and methodology for the EPIC-Norfolk study has previously been described [27]. To summarise, general practice age-sex registers were used to identify participants, representative of the UK population [27], who were invited to complete a baseline questionnaire, health check, biospecimen collection and nutrition assessment between 1993 and 1997. Regular health checks and further assessments were conducted regularly over the next 25 years. Second health check (2HC - 1998-2000) included bone health assessment, and third health check (3HC - 2004-2011) assessed participants' physical capabilities.

2.2. Predictor variable

During the bone health assessment in 2HC from 1998 to 2000, participants' bone strength was evaluated using broadband (i.e. calcaneal) ultrasound attenuation (BUA) using a contact ultrasound bone analyser (CUBA) device [28]. BUA can as accurately discriminate low bone strength as dual-energy X-ray absorptiometry (DEXA) [29]. CUBA devices were calibrated regularly [30], and BUA measures were at least duplicated for each foot, with mean BUA from right and left foot measures used for this analysis.

For this study purpose, low BUA was defined as a mean BUA less than one sex-specific standard deviation (SD) below the sex-specific population mean. This definition follows from previous studies which showed fracture risk to double for every SD decrease below the young-adult mean [23,31,32].

2.3. Outcome variable

Physical performance was evaluated by creating a summary performance score (SPS) by summating categorical rankings of the scores for the tests of standing balance, gait speed, and repeatedly rising from a chair 5 times, measured during 3HC from 2004 to 2011. SPS scores range from 3 to 12, where SPS 3–6 is considered low. Low SPS has previously been demonstrated to be highly predictive of subsequent disability, functional decline depicted by admission to nursing homes and mortality in older adults [6,33,34].

2.4. Covariates

Covariates were pre-selected based on literature review findings. Age, sex and body mass index (BMI) were recorded during 2HC of the study using a standardised protocol [35]. Cigarette smoking status was obtained and reclassified into 'former or current smoker' and 'never smoker'. Likewise, average weekly alcohol consumption was reclassified into 'consumes $<$7 units alcohol per week' and 'consumes $\geq$ 7 units alcohol per week' for the purposes of this study. Physical activity (expressed as active, moderately active, moderately inactive, inactive) assessed by a validated patient questionnaire [36], was recorded and reclassified into the two categories of 'active' and 'inactive'.

Lower socioeconomic status, associated with suboptimal bone health [37,38], was determined using three measures (occupational social class; educational attainment; and Townsend Deprivation Index (TDI)). For the purpose of this study, social class was categorised into two broad groups based on whether a participant or their partner had a manual/ non-manual occupation [27]. Education status was also split into two groups based on highest qualification achieved: (1) Degree and/or A-level/equivalent; (2) O-level/equivalent or less. O-level is usually indicative of minimum academic achievement of the UK school leaving age. TDI, a multi-factor scoring system evaluating deprivation of an area where 0 is the national mean, classified study participants into '0 or less' and 'above 0'. Negative scores represent lower deprivation, and positive scores signify greater deprivation [39].

During all phases of the study, participants were asked to disclose of medically diagnosed illnesses (e.g. stroke), hormone therapy or steroid use in regular health questionnaires.

2.5. Statistical analyses

Analyses were conducted using SPSS version 26.0 (IBM, New York, USA). Participants with missing data for BUA, physical capabilities or covariates required for the models were excluded. Participants with a cancer diagnosis were also excluded. All analyses were stratified by sex; there are sex-specific differences in BUA measures, and there are clear differences in physical capability between sex [6,31,34].

Study characteristics were described using proportions (for categorical data), means and medians (for normally and non-normally distributed continuous data). Differences between BUA and SPS were compared using the *t*-test or Mann-Whitney test for continuous variables, or the Pearson Chi-squared test for categorical variables.

2.5.1. BUA as a continuous predictor of SPS

The relationship between decreasing BUA and SPS were explored using sex-specific linear regression models. SPS was considered a continuous outcome measure for every 5 point decrease in BUA. The unstandardised β-coefficients were calculated with the standard of error (SE) for each 5 point decrease in BUA and presented with p-values. p-Values of less or equal to 0.05 were deemed statistically significant.

2.5.2. BUA as a categorical predictor of low physical performance

Associations between low BUA ($<$1 sex-specific SD below the sex-specific mean) and low physical performance (SPS 3–6) were explored using logistic regression using multivariate sub-analysis to determine whether potential confounders may attenuate any observed relationships. Odds ratios (OR) were presented with 95 confidence intervals (95 % CI).

Characteristics were pre-selected to stratify each analyses based on evidence suggesting BUA and physical capability vary with age [34,40], BMI [5,40], socioeconomic factors [41,42], health behaviours [7,43], concurrent medication use [44,45], and prevalent stroke [41]. Six models considering each aforementioned category were used to examine the relationships: Model A was unadjusted; model B adjusted for age and sex; model C additionally adjusted for social class, education level and TDI; model D additionally adjusted for smoking, alcohol consumption and physical activity; model E further adjusted for hormone therapy (in women only) and steroid use; and model F also considered prevalent stroke as this will likely reduce physical capability.

We adopted a cross-sectional analysis approach since our outcome is a measurement, rather than a time-dependent incident/event such as mortality. We therefore used linear and logistic regression models instead of Cox-regression models, despite the prospective nature of the exposure-outcome relationship.

3. Results

3.1. Main findings

Of the 8583 EPIC-Norfolk participants who completed 3HC, 1863 had missing or incomplete data for BUA. A further 827 participants with a cancer diagnosis were excluded, leaving a final sample of 5893 participants (55.8 % women). The mean (SD) age at 2HC was 59.1 (7.9) years.

Table 1 shows the distribution of sample characteristics by BUA status. Overall, the population has a low level of deprivation and obesity, and consists of individuals of high educational and occupational status. Other than a significant association between lower BMI and low BUA, there were no significant differences in characteristics between men with low and normal BUA. However, for women there were highly significant differences; increased age, lower BMI, lower measures of physical capability (standing balance, gait speed, time to complete 5 chair rises) and SPS, greater deprivation and lower prevalence of HRT use were significantly associated with low BUA.

Participants had SPS ranging from 3 to 12. More than half both men and women participants had a SPS of 9 or greater. The distribution of summary performance score (SPS) among men and women is shown in Fig. 1.

3.2. BUA as a continuous predictor of SPS

Table 2 shows the sex-specific linear regression models for change in SPS by every 5-point decrease in BUA. In model A for men, a 5-point lower BUA measure corresponds with a 0.26 lower average SPS. The multivariate model F had β-coefficient (SE) -0.22 (0.01) ($p = 0.01$). In women, a 5-point decrease in BUA corresponded with a 0.85 lower SPS in model A, although the association weakened in the multivariate model F (β-coefficients (SE) -0.20 (0.02) ($p = 0.02$)).

3.3. BUA as a categorical predictor of low physical performance

The OR and 95 % CI representing associations between low BUA (BUA <1SD below sex-specific mean) and low physical performance (SPS 3–6) are displayed in Table 3. There were 368 men and 325 women with low BUA, and 1478 men and 2759 women with normal BUA. There was a consistent association between low BUA and poor physical performance in women in all models, with an OR (95 % CI) of 1.35 (1.01, 1.84) in the fully-adjusted model, model F. None of the associations were significant in men (multivariable model: OR 0.84 (95 % CI 0.59, 1.19)).

When the sample was stratified by age (<65 (reference) vs. 65 and over), both men and women who were 65 years or older compared to their younger counterparts had significantly higher odds of subsequent low physical performance (defined as SPS 3–6) if they had low BUA (defined as BUA <1SD below sex-specific mean) at baseline: the OR (95 % CI) for fully adjusted model (model F) was 5.77 (4.30–7.64) for men and 5.54 (4.42–6.93) for women, respectively.

Similarly, stratifying by BMI (<30 (reference) vs. 30 and over) highlighted that both men and women of greater BMI had significantly higher odds of low physical performance compared to those with lower BMI if they had low BUA at baseline: OR (95 % CI) for model F was 2.85 (1.98–4.09) for men and 2.08 (1.58–2.72) for women.

When considering socioeconomic factors, stratifying the population by social class (non-manual workers (reference) vs. manual workers)

Table 1
Characteristics of 1841 men and 3084 women EPIC Norfolk participants by BUA status.

Characteristics	Men			Women		
	Low BUA	Normal BUA	p value	Low BUA	Normal BUA	p value
	N = 367	N = 1474		N = 325	N = 2759	
Mean (SD)						
Age in years	59.7 (8.4)	60.2 (7.8)	0.27[b]	64.3 (7.6)	57.7 (7.5)	<0.001[b]
BMI in kg/m^2	25.9 (3.0)	26.5 (3.2)	<0.001[b]	24.7 (3.5)	26.1 (4.1)	<0.001[b]
Maximum grip strength in kg	38.4 (8.0)	38.8 (8.2)	0.44[b]	22.1 (5.2)	24.7 (5.4)	<0.001[b]
Gait speed in s	3.8 (1.1)	3.7 (1.0)	0.20[b]	4.5 (3.2)	3.9 (1.5)	<0.001[b]
Summary performance score (SPS)	8.5 (2.2)	8.6 (2.3)	0.59[b]	7.5 (2.6)	8.6 (2.3)	<0.001[b]
Median (IQR)						
Time to complete 5 chair rises in s	12.0 (9.5–14.4)	11.8 (9.7–14.3)	0.98[c]	12.8 (10.9–16.1)	11.9 (10.0–14.4)	<0.001[c]
Frequency, % (n)						
Smoking status						
Never smoker	37.9 (139)	41.9 (617)	0.17[a]	38.4 (124)	38.0 (1043)	0.89[a]
Alcohol consumption						
<7 units/week	49.9 (182)	48.0 (702)	0.53[a]	74.8 (237)	71.6 (1935)	0.24[a]
Social class						
Manual worker	38.3 (141)	35.3 (521)	0.27[a]	34.8 (113)	32.9 (908)	0.50[a]
Highest education status						
0-levels or lower	32.6 (119)	33.0 (485)	0.88[a]	46.2 (150)	42.0 (1159)	0.15[a]
Deprivation (Townsend Index >0)	14.7 (54)	14.4 (212)	0.88[a]	18.2 (59)	13.8 (379)	0.03[a]
Physical activity						
Active	63.0 (228)	64.0 (934)	0.73[a]	51.7 (166)	56.5 (1537)	0.10[a]
Steroid use at 2HC	3.8 (14)	3.0 (44)	0.42[a]	4.3 (14)	3.7 (101)	0.56[a]
Low SPS	16.8 (62)	18.2 (269)	0.54[a]	34.2 (111)	19.0 (524)	<0.001[a]
Ever used hormone therapy?	–	–		29.8 (96)	47.0 (1283)	<0.001[a]
Prevalent stroke	2.2 (8)	1.6 (23)	0.39[a]	1.5 (5)	0.9 (25)	0.25[a]

p-Value as calculated by Chi-squared test[a], independent samples t-test[b] and Mann-Whitney test[c].
Abbreviations: BUA, broadband ultrasound attenuation; SD, standard deviation; IQR, interquartile range; BMI, body mass index; HRT, hormone replacement therapy; 2HC, second health check.

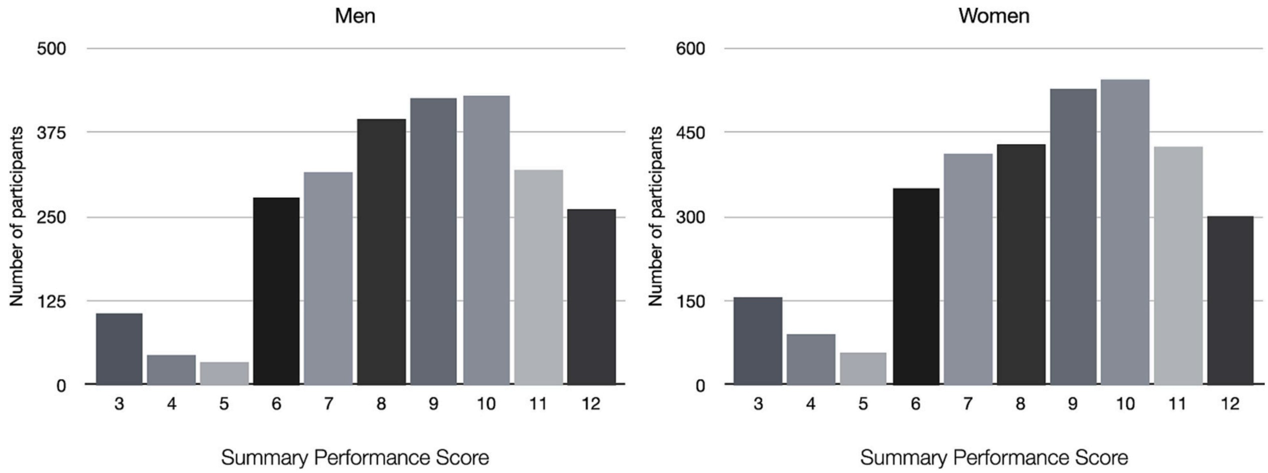

Fig. 1. Summary performance score (SPS) distribution among 6288 EPIC-Norfolk participants.
The summary performance score was created by summing categorical rankings of the scores for the tests of standing balance, gait speed, and repeatedly rising from a chair 5 times.

Table 2
The β-coefficient (standard error (SE)) of linear regression model for change in summary performance score (SPS) by every 5-point decrease in BUA in 1841 men and 3084 women, with and without adjustment.

	β-Coefficient (SE)	p-Value
Men		
Model A	−0.26 (0.02)	0.009
Model B	−0.26 (0.01)	0.003
Model C	−0.25 (0.01)	0.005
Model D	−0.23 (0.01)	0.01
Model E	−0.22 (0.01)	0.01
Model F	−0.22 (0.01)	0.01
Women		
Model A	−0.85 (0.02)	<0.001
Model B	−0.26 (0.01)	0.002
Model C	−0.23 (0.01)	0.007
Model D	−0.20 (0.02)	0.02
Model E	−0.20 (0.02)	0.02
Model F	−0.20 (0.02)	0.02

Model A: unadjusted model. Model B: adjusted for age and BMI. Model C: as model B, additionally adjusted for social class, educational level and TDI. Model D: as model C, additionally adjusted for smoking status, alcohol consumption and physical activity. Model E: as model D, additionally adjusted for hormone and steroid therapy. Model F: as model E, additionally adjusted for prevalent stroke.
Abbreviations: SPS, summary performance score; BUA, broadband ultrasound attenuation; SE, standard error; TDI, Townsend Deprivation Index.

suggested manual workers who were men had significantly increased odds of future low physical capability if they had low BUA at baseline: OR (95 % CI) for model F was 1.59 (1.19–2.13). This was not significant in the fully-adjusted model for women: Model F OR (95 % CI) was 1.23 (0.98–1.54). However, women with a lower education status compared to those with a higher education status (O-level or less vs. A-level or above (reference)) had significantly higher odds of low physical performance if they had low BUA at baseline: OR (95 % CI) for model F was 1.42 (1.15–1.76). All models in men exploring education level were not significant, with model F OR (95 % CI) 1.12 (0.83–1.50). Interestingly, stratifying by deprivation (TDI ≤ 0 (i.e. low deprivation) (reference) vs. TDI > 0 (i.e. higher deprivation)) showed men living in an area of higher deprivation were at significantly lower odds of low physical capability compared to those living in an area of lower deprivation if they had low BUA at baseline: OR (95 % CI) for model F was 0.61 (0.39–0.93). This was not evident among women where all models showed no association: OR (95 % CI) for model F was 1.17 (0.87–1.56).

When health behaviours were explored, stratifying the population by smoking (never (reference) vs. current or previous) and alcohol consumption (<7 units/week (reference) vs. ≥ 7 units/week) yielded no significant findings: The fully-adjusted models (model F) for smoking were OR (95 % CI) 1.29 (0.96–1.74) for men and 0.86 (0.69–1.07) for women, respectively. For alcohol consumption these were OR (95 % CI) 0.84 (0.63–1.11) among men and 0.87 (0.68–1.11) among women, respectively. When stratifying by physical activity (active (reference) vs. inactive), both men and women who were deemed to be inactive had significantly higher odds of future low physical performance if they had low BUA at study baseline: the OR (95 % CI) for model F was 1.64 (1.24–2.17) for men and 1.27 (1.04–1.57) for women, respectively.

Stratifying by concurrent steroid use (no (reference) vs. yes) showed no association for men: Model F OR (95 % CI) 1.45 (0.73–2.90). Women who were exposed to steroids were at significantly higher odds of subsequent low physical performance if they had low BUA at baseline compared to those not exposed to steroids: OR (95 % CI) for the fully-adjusted model (model F) was 2.05 (1.29–3.27). Women who had used hormone therapy (no (reference) vs. yes) were not found to have any increased or decreased association with future low physical performance if they had low BUA at baseline: OR (95 % CI) for model F was 1.15 (0.93–1.44).

When the sample was stratified by prevalent stroke (no (reference) vs. yes), women who previously had a stroke compared to those who had not, were at significantly higher odds of future low physical capability if they had low BUA at baseline: OR (95 % CI) was 2.74 (1.12–6.74). No association was apparent in men: OR (95 % CI) was 0.77 (0.29–2.06).

The interactions between sex and age were investigated in logistic regression unstratified analyses and were significant (p-value <0.001), suggesting that the relationship between BUA and physical performance differed with sex and age.

4. Discussion

4.1. Main findings

As poor physical capability is associated with adverse health outcomes, early detection is an attractive proposition. We found that among EPIC-Norfolk cohort participants, lower BUA measures were associated with poorer future physical capability at a univariate and multivariate level, independent of age, BMI, socioeconomic factors, health behaviours, and medications, especially among women. These findings coincide with evidence that superior bone strength in middle-late adulthood is protective against rapid deterioration in physical health [22,46,47].

Several cohort studies, similar to the present study but examining the

Table 3
Odds of low physical performance (SPS 3–6) by low BUA, older age, higher BMI, manual social class, lower education level, higher deprivation, positive smoking history, greater alcohol consumption, low physical activity, steroid use, hormone therapy use (women only) and prevalent stroke compared to their counterparts, in EPIC-Norfolk cohort.

	N (%)	Odds ratio (95 % confidence interval)					
		Model A	Model B	Model C	Model D	Model E	Model F
Men							
BUA							
Normal	1478 (80.1)	1.00	1.00	1.00	1.00	1.00	1.00
Low	368 (19.9)	0.91 (0.67–1.23)	0.91 (0.66–1.26)	0.91 (0.65–1.26)	0.87 (0.62–1.22)	0.87 (0.62–1.22)	0.84 (0.59–1.19)
Age (years)		–					
<65	1283 (69.6)		1.00	1.00	1.00	1.00	1.00
≥65	561 (30.4)		6.39 (4.93–8.29)**	6.64 (5.09–8.67)**	6.20 (4.74–8.12)**	6.17 (4.71–8.08)**	5.77 (4.3–7.64)**
BMI		–					
<30	1628 (88.3)		1.00	1.00	1.00	1.00	1.00
≥30	216 (11.7)		2.91 (2.06–4.11)**	2.96 (2.08–4.19)**	2.83 (1.98–4.02)**	2.83 (1.99–4.03)**	2.85 (1.98–4.09)**
Social class		–	–				
Non-manual	1181 (64.6)			1.00	1.00	1.00	1.00
Manual	647 (35.4)			1.52 (1.16–2.00)*	1.58 (1.20–2.09)*	1.59 (1.20–2.10)*	1.59 (1.19–2.13)*
Education level		–	–				
A-level or above	1227 (67.1)			1.00	1.00	1.00	1.00
None or O-level	601 (32.9)			1.17 (0.89–1.54)	1.15 (0.87–1.52)	1.16 (0.88–1.53)	1.12 (0.83–1.50)
Deprivation		–	–				
TDI ≤ 0	1568 (85.8)			1.00	1.00	1.00	1.00
TDI >0	260 (14.2)			0.62 (0.42–0.93)*	0.58 (0.39–0.88)*	0.58 (0.39–0.88)*	0.61 (0.39–0.93)*
Smoking							
Never	743 (41.4)	–	–	–	1.00	1.00	1.00
Current or previous	1051 (58.6)				1.23 (0.93–1.63)	1.23 (0.93–1.63)	1.29 (0.96–1.74)
Alcohol consumption							
<7 units/week	869 (48.4)	–	–	–	1.00	1.00	1.00
≥7 units/week	925 (51.6)				0.86 (0.66–1.13)	0.86 (0.66–1.13)	0.84 (0.63–1.11)
Physical activity							
Active	1143 (63.7)	–	–	–	1.00	1.00	1.00
Inactive	651 (36.3)				1.58 (1.21–2.07)**	1.58 (1.20–2.06)**	1.64 (1.24–2.17)**
Steroid use at 2HC							
No	1737 (96.8)	–	–	–	–	1.00	1.00
Yes	57 (3.2)					1.31 (0.68–2.55)	1.45 (0.73–2.90)
Prevalent stroke							
No	1671 (98.3)	–	–	–	–	–	1.00
Yes	29 (1.7)						0.77 (0.29–2.06)
Women							
BUA							
Normal	2759 (89.5)	1.00	1.00	1.00	1.00	1.00	1.00
Low	325 (10.5)	2.21 (1.73–2.84)**	1.44 (1.10–1.90)*	1.41 (1.07–1.85)*	1.33 (1.01–1.77)*	1.37 (1.03–1.83)*	1.35 (1.01–1.84)*
Age (years)		–					
<65	2334 (75.8)		1.00	1.00	1.00	1.00	1.00
≥65	747 (24.2)		5.14 (4.22–6.25)**	5.30 (4.35–6.46)**	5.21 (4.26–6.39)**	5.44 (4.40–6.72)**	5.54 (4.42–6.93)**
BMI		–					
<30	2642 (85.8)		1.00	1.00	1.00	1.00	1.00
≥30	439 (14.2)		2.37 (1.87–3.02)**	2.22 (1.74–2.83)**	2.19 (1.71–2.82)**	2.15 (1.67–2.76)**	2.08 (1.58–2.72)**
Social class		–	–				
Non-manual	2053 (67.4)			1.00	1.00	1.00	1.00
Manual	993 (32.6)			1.37 (1.12–1.67)*	1.30 (1.05–1.60)*	1.31 (1.06–1.62)*	1.23 (0.98–1.54)
Education level		–	–				

(*continued on next page*)

Table 3 (*continued*)

	N (%)	Odds ratio (95 % confidence interval)					
		Model A	Model B	Model C	Model D	Model E	Model F
A-level or above	1755 (57.6)			1.00	1.00	1.00	1.00
O-level or less	1291 (42.4)			1.41 (1.16–1.71)**	1.42 (1.16–1.73)**	1.41 (1.16–1.73)**	1.42 (1.15–1.76)*
Deprivation		–	–				
TDI ≤ 0	2615 (85.8)			1.00	1.00	1.00	1.00
TDI >0	431 (14.2)			1.17 (0.90–1.52)	1.11 (0.85–1.45)	1.11 (0.85–1.46)	1.17 (0.87–1.56)
Smoking							
Never	1838 (62.2)	–	–	–	1.00	1.00	1.00
Current or previous	1115 (37.8)				0.92 (0.75–1.12)	0.90 (0.73–1.11)	0.86 (0.69–1.07)
Alcohol consumption							
<7 units/week	2128 (72.1)	–	–	–	1.00	1.00	1.00
≥7 units/week	825 (27.9)				0.89 (0.71–1.12)	0.88 (0.70–1.11)	0.87 (0.68–1.11)
Physical activity							
Active	1648 (55.8)	–	–	–	1.00	1.00	1.00
Inactive	1305 (44.2)				1.26 (1.04–1.53)*	1.26 (1.04–1.53)*	1.27 (1.04–1.57)*
Steroid use at 2HC							
No	2812 (96.1)	–	–	–	–	1.00	1.00
Yes	113 (3.9)					2.03 (1.32–3.14)*	2.05 (1.29–3.27)*
Ever used hormone therapy?							
No	1612 (55.1)	–	–	–	–	1.00	1.00
Yes	1313 (44.9)					1.19 (0.97–1.46)	1.15 (0.93–1.44)
Prevalent stroke							
No	2668 (99.1)	–	–	–	–	–	1.00
Yes	25 (0.9)						2.74 (1.12–6.74)*

Model A: unadjusted model. Model B: adjusted for age and BMI. Model C: as model B, additionally adjusted for social class, educational level and TDI. Model D: as model C, additionally adjusted for smoking status, alcohol consumption and physical activity. Model E: as model D, additionally adjusted for hormone and steroid therapy. Model F: as model E, additionally adjusted for prevalent stroke.

Abbreviations: SPS, summary performance score; BUA, broadband ultrasound attenuation; OR, odds ratio; CI, confidence interval; 2HC, second health check.

$p < 0.05$.

** $p < 0.001$.

* $p \geq 0.001$.

reverse association, have found physical capability to be a strong indicator of bone and muscle strength [48–52], as these two factors are closely related [53]. These, combined with our findings suggesting bone strength measures can predict future physical capability, highlights a downward spiral effect where poor bone and muscle health leads to reduced physical capability, which further compromises bone and muscle strength, and so on. This study, being the first to demonstrate this link, further suggests that non-physical reasons for inadequate bone strength, such as increasing age, low BMI and dietary factors [54], could subsequently lead to reduced physical capability, and the associated undesirable health outcomes, by way of this downward spiral.

Our findings suggest differences in the relationship between low BUA and physical capability by sex. At a characteristics level, SPS was significantly different among individuals with low and normal BUA in women only. When both BUA and SPS were considered as continuous predictor and outcome variables, a greater association between BUA and SPS was evident in men than women. Conversely, when both were considered as categorical variables, and relationships between low BUA and low physical performance were considered, no relationship existed for men. This may be because men have significantly greater BUA measures compared to women [42], therefore defining 'low BUA' as BUA <1SD below the sex-specific mean will likely overestimate the proportion of men with inadequate BUA. Incidence of low BUA is also less frequent among men than women [42]. As a consequence, categorical outcomes will show stronger associations for women, although linear relationships between decreased BUA in men may be a stronger marker of low physical performance than in women.

This study has identified risk factors for reduced physical capability, confirming what we already know (such as age, BMI and physical inactivity), whilst providing a clearer picture regarding the differing risk factors for men and women – in addition to a potential method of identifying these individuals by use of BUA. Lower social class (i.e. manual occupation) was significantly associated with reduced physical performance in men. Contrary to this, higher deprivation (TDI $>$ 0) was found to be significantly protective against low physical performance in men. TDI is based on postcode, reflecting the deprivation of an area rather than an individual's income; therefore none-deprived individuals may be incorrectly considered to be deprived by TDI. It is likely that small sample sizes, increasing risk of chance findings, may also be accountable for this finding. Lower education level, steroid use and prevalent stroke were identified as a risk factor for subsequent low physical capability in those with low BUA at baseline for women, but not for men. Sex-differences in risk factors have also been noted by several studies investigating BUA and osteoporosis risk [16], components of frailty (including physical capability measures) [46], and future health outcomes [47]. Men have greater bone size and skeletal mass than women [40], therefore BUA among men and women is distinctly different, as are the associated physical capabilities and health measures. Older obese women are more likely to be frail [55], despite adequate BUA. In women, obesity is protective against rapid bone mass deterioration after menopause due to increased oestrogens production by adipose tissue and greater mechanical loading [30,56]. However, older underweight men are more likely to be frail and have low BUA [55]. These differences are clearly reflected in our findings, and highlight the importance of stratifying study populations by sex when using BUA as a predictor.

A BUA score of less than one sex-specific SD below the sex-specific mean was a weak to moderate predictor of low physical performance (SPS 3–6) in women only, where having low BUA equates to having a lower education level and a manual occupation. Approximately 18 % men and 20 % women had SPS 3–6 in our study, which is associated with up to a five times increased risk of mobility-related disability at four years follow-up compared to people with SPS scores 10–12 [6]. Furuna et al. found older adults with low SPS were less likely to maintain ADLs at four years [34]. Considering the three attributes of SPS (gait speed, timed chair rises and standing balance), women perform worse than men even after adjustment for age and anthropometric measurements [4]. This observation is known as the male-female health-survival paradox [57]; women have longer life expectancies, yet poor physical capability is associated with higher mortality.

4.2. Clinical relevance

Given that older adults constitute the world's fastest growing population, risk assessment and prediction of physical health deterioration is vital [23]. Screening of poorer future physical capability provided by a simple one-off BUA measure could allow for early lifestyle and pharmacological interventions to be made before further decline in health [24–26]. Furthermore, it may be used to stratify populations into those requiring full frailty assessment. BUA could potentially predict other important measures in the ageing population besides physical capability and osteoporosis/fracture risk, such as falls and sarcopenia, and therefore warrants further evaluation.

4.3. Strengths

To our knowledge, this study is the first to investigate BUA as a predictor of future physical capability in older adults, allowing for early identification of people at risk of numerous health outcomes. We used a large population-based cohort with validated follow-up methods [27], with the ability to control for a range of confounders including sociodemographic and lifestyle factors. Data were collected prospectively, minimising potential for recall bias, with adequate follow-up (at least six years), limiting potential for reverse causality, over a critical period of time in the participants' lives when physical capability typically deteriorates. This highlights the effectiveness of BUA as an early, inexpensive, and non-invasive indicator of physical capability among women, potentially able to indicate risk of numerous outcomes including physical disability [6], sarcopenia [4,11], frailty [12,13] and mortality [5,9].

4.4. Limitations

Given that EPIC-Norfolk is a volunteer study consisting of predominantly white, middle-class health-conscious individuals, the existence of healthy volunteer bias is possible. Despite this, sample characteristics of EPIC-Norfolk are reported to be representative of the UK population [27]. Given the relative homogeneity of the study population, some risk factors of poor physical capability and bone ageing, such as race [16], cannot be evaluated. Furthermore, this analysis only includes participants who remained in the EPIC-Norfolk study for at least six years, potentially giving rise to survivor bias. Those at baseline who were older, heavier, smokers and hypertensive were more likely to drop out of the study [58]. As this is a secondary data analysis of an observational study, unknown residual confounding is possible, and confounders may vary over time – such as BMI. Missing BUA data decreased sample size, however missing BUA data was at random and should not compromise study findings. Time between BUA and physical capability measures varied among participants, ranging from six to eleven years. This variation may impact on validity of findings, as it is not uniform among participants.

4.5. Further research

The use of BUA as a predictor of important outcomes in the ageing population is a relatively new concept. With the potential to predict numerous health outcomes in addition to physical capability, further evaluation is required among both men and women, especially with regard to its use as a screening tool in clinical practice.

5. Conclusion

In conclusion, BUA is an easy and inexpensive tool capable of predicting future physical capability in an apparently healthy population of older adults. With the ageing population continuing to rise, tools like BUA to stratify populations at risk of age-related poor health are required to allow for early intervention and individual and public health planning. Further validation is required to evaluate the use of BUA as a screening tool to detect poor physical capability in clinical practice.

Contributors

Sarah L Perrott performed the literature review and statistical analysis, and produced the first draft of the paper.
Kathryn Martin contributed to the study conception.
Victoria L Keevil contributed to the study conception.
Nicholas J Wareham was a principal investigator in the study.
Kay-Tee Khaw was a principal investigator in the study.
Phyo Kyaw Myint contributed to the study conception.
All authors read and reviewed the final manuscript.

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Ethical approval

The EPIC-Norfolk study was approved by the Norwich Research Ethics Committee.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request to the steering committee of EPIC-Norfolk.

Declaration of competing interest

Sarah Perrott, Kathryn Martin, Victoria L Keevil, Nicholas J Wareham, Kay-Tee Khaw, and Phyo Kyaw Myint declare that they have no competing interests.

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References

[1] United Nations, World population pyramid. https://www.populationpyramid.net/world/2050/, 2022. (Accessed 19 February 2022).
[2] C.B. Newgard, N.E. Sharpless, Coming of age: molecular drivers of aging and therapeutic opportunities, J. Clin. Invest. 123 (2013) 946–950, https://doi.org/10.1172/JCI68833.
[3] E. Kanasi, S. Ayilavarapu, J. Jones, The aging population: demographics and the biology of aging, Periodontol. 2000 (72) (2016) 13–18, https://doi.org/10.1111/prd.12126.
[4] V.L. Keevil, S. Hayat, N. Dalzell, S. Moore, A. Bhaniani, R. Luben, N.J. Wareham, K. T. Khaw, The physical capability of community-based men and women from a british cohort: the european prospective investigation into cancer (EPIC)-Norfolk study, BMC Geriatr. 13 (2013) 1–11, https://doi.org/10.1186/1471-2318-13-93.
[5] R. Cooper, D. Kuh, R. Hardy, Objectively measured physical capability levels and mortality: systematic review and meta-analysis, BMJ 341 (2010) 639, https://doi.org/10.1136/bmj.c4467.
[6] J.M. Guralnik, L. Ferrucci, C.F. Pieper, S.G. Leveille, K.S. Markides, G.V. Ostir, S. Studenski, L.F. Berkman, R.B. Wallace, Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery, J. Gerontol. A Biol. Sci. Med. Sci. 55 (2000) 221–231, https://doi.org/10.1093/gerona/55.4.M221.
[7] M.E. Tinetti, M. Speechley, S.F. Ginter, Risk factors for falls among elderly persons living in the community, N. Engl. J. Med. 319 (1988) 1701–1707, https://doi.org/10.1056/NEJM198812293192604.
[8] N.C. Harvey, A. Od, E. Orwoll, J. Lapidus, T. Kwok, M.K. Karlsson, Measures of physical performance and muscle strength and aBMD: a meta-analysis of the osteoporotic fractures in men (MrOS) study, Am. Soc. Bone Miner. Res. 33 (2018) 2150–2157, https://doi.org/10.1002/jbmr.3556.
[9] R. Matsuzawa, K. Kamiya, N. Hamazaki, K. Nozaki, S. Tanaka, E. Maekawa, A. Matsunaga, T. Masuda, J. Ako, Office-based physical assessment in patients aged 75 years and older with cardiovascular disease, Gerontology 65 (2019) 128–135, https://doi.org/10.1159/000493527.
[10] D.X.M. Wang, J. Yao, Y. Zirek, E.M. Reijnierse, A.B. Maier, Muscle mass, strength, and physical performance predicting activities of daily living: a meta-analysis, J. Cachexia. Sarcopenia Muscle 11 (2020) 3–25, https://doi.org/10.1002/jcsm.12502.
[11] S.N. Mohd Nawi, K.S. Khow, W.S. Lim, S.C. Yu, Screening tools for sarcopenia in community-dwellers: a scoping review, Ann. Acad. Med. Singap. 48 (2019) 201–216.
[12] M. Sayol Carol, L. Bajo Peñas, L. Boix Sala, M. Bajo Peñas, J. Altimiras Roset, J. Amblàs Novellas, Applicability and limitations of physical performance tests for frailty screening on discharge from an intermediate care hospital, Rev. Esp. Geriatr. Gerontol. 55 (2020) 212–215, https://doi.org/10.1016/j.regg.2020.02.002.
[13] L.L.G. Rocco, T.G. Fernandes, Validity of the short physical performance battery for screening for frailty syndrome among older people in the Brazilian Amazon region. A cross-sectional study, Sao Paulo Med. J. 138 (2020) 537–544, https://doi.org/10.1590/1516-3180.2020.0264.R1.14092020.
[14] P. Ponvel, S. Shahar, D.K.A. Singh, A.F.M. Ludin, R. Rajikan, N.F. Rajab, C. Ai-Vyrn, N.C. Din, N. Ibrahim, P. Subramaniam, H. Haron, A. Ismail, R. Sharif, K. Ramasamy, A.B.A. Majeed, N.M. Ali, M. Mohamad, S.A.M. Noah, A.M. Ibrahim, A.M. Safien, N.M. Khalid, N.H.M. Fadzil, F. Mangialasche, M. Kivipelto, Multidomain intervention for reversal of cognitive frailty, towards a personalized approach (AGELESS Trial): study design, J. Alzheimers Dis. 82 (2021) 673–687, https://doi.org/10.3233/JAD-201607.
[15] C. Li, J. Sun, L. Yu, Diagnostic value of calcaneal quantitative ultrasound in the evaluation of osteoporosis in middle-aged and elderly patients, Medicine (Baltimore) 101 (2022), https://doi.org/10.1097/MD.0000000000028325 e28325-e28325.
[16] K. Thomsen, D.B. Jepsen, L. Matzen, A.P. Hermann, T. Masud, J. Ryg, Is calcaneal quantitative ultrasound useful as a prescreen stratification tool for osteoporosis? Osteoporos. Int. 26 (2015) 1459–1475, https://doi.org/10.1007/s00198-014-3012-y.
[17] C.M. Langton, The 25th anniversary of BUA for the assessment of osteoporosis: time for a new paradigm? Proc. Inst. Mech. Eng. Part H J. Eng. Med. 225 (2011) 113–125, https://doi.org/10.1243/09544119JEIM777.
[18] M.J. Cook, A. Oldroyd, S.R. Pye, K.A. Ward, E. Gielen, R. Ravindrarajah, J. E. Adams, D.M. Lee, G. Bartfai, S. Boonen, F. Casanueva, G. Forti, A. Giwercman, T. S. Han, I.T. Huhtaniemi, K. Kula, M.E. Lean, N. Pendleton, M. Punab, D. Vanderschueren, F.C. Wu, T.W. O'Neill, L. Petrone, A. Cilotti, H. Borghs, J. Slowikowska-Hilczer, R. Walczak-Jedrzejowska, A. Silman, J. Finn, P. Steer, A. Tajar, M. Ocampo, M. Lage, I. Földesi, I. Fejes, P. Korrovitz, M. Jiang, Frailty and bone health in european men, Age Ageing 46 (2017) 635–641, https://doi.org/10.1093/ageing/afw205.
[19] G. Ioannidis, A. Papaioannou, W.M. Hopman, N. Akhtar-Danesh, T. Anastassiades, L. Pickard, C.C. Kennedy, J.C. Prior, W.P. Olszynski, K.S. Davison, D. Goltzman, L. Thabane, A. Gafni, E.A. Papadimitropoulos, J.P. Brown, R.G. Josse, D.A. Hanley, J.D. Adachi, Relation between fractures and mortality: results from the Canadian multicentre osteoporosis study, CMAJ 181 (2009) 265–271, https://doi.org/10.1503/cmaj.081720.
[20] L.J. Melton 3rd, S.J. Achenbach, E.J. Atkinson, T.M. Therneau, S. Amin, Long-term mortality following fractures at different skeletal sites: a population-based cohort study, Osteoporos. Int. 24 (2013) 1689–1696, https://doi.org/10.1007/s00198-012-2225-1.
[21] R. Hasserius, M.K. Karlsson, B.E. Nilsson, I. Redlund-Johnell, O. Johnell, Prevalent vertebral deformities predict increased mortality and increased fracture rate in both men and women: a 10-year population-based study of 598 individuals from the swedish cohort in the european vertebral osteoporosis study, Osteoporos. Int. 14 (2003) 61–68, https://doi.org/10.1007/s00198-002-1316-9.
[22] C. Pongchaiyakul, N.D. Nguyen, G. Jones, J.R. Center, J.A. Eisman, T.V. Nguyen, Asymptomatic vertebral deformity as a major risk factor for subsequent fractures and mortality: a long-term prospective study, J. Bone Miner. Res. 20 (2005) 1349–1355, https://doi.org/10.1359/JBMR.050317.
[23] N.E. Lane, Epidemiology, etiology, and diagnosis of osteoporosis, Am. J. Obstet. Gynecol. 194 (2006), https://doi.org/10.1016/j.ajog.2005.08.047.
[24] R.M. Daly, J. Dalla Via, R.L. Duckham, S.F. Fraser, E.W. Helge, Exercise for the prevention of osteoporosis in postmenopausal women: an evidence-based guide to the optimal prescription, Braz. J. Phys. Ther. 23 (2019) 170–180, https://doi.org/10.1016/j.bjpt.2018.11.011.
[25] M. Posch, A. Schranz, M. Lener, K. Tecklenburg, M. Burtscher, G. Ruedl, M. Niedermeier, W. Wlaschek, Effectiveness of a mini-trampoline training program on balance and functional mobility, gait performance, strength, fear of falling and bone mineral density in older women with osteopenia, Clin. Interv. Aging 14 (2019) 2281–2293, https://doi.org/10.2147/CIA.S230008.
[26] J.K.H. Luk, T.Y. Chan, D.K.Y. Chan, Falls prevention in the elderly: translating evidence into practice, Hong Kong Med. J. 21 (2015) 165–171, https://doi.org/10.12809/hkmj144469.
[27] N.W.N. Day, S. Oakes, R. Luben, K.T. Khaw, S. Bingham, A. Welch, EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer, Br. J. Cancer 80 (1999) 95–103.
[28] The EPIC-Norfolk study: second health check (2HC), Univ. Cambridge, 2021. https://www.epic-norfolk.org.uk/about-epic-norfolk/health-checks/second-health-check-2hc/. (Accessed 6 March 2021).
[29] Y.Q. He, B. Fan, D. Hans, J. Li, C.Y. Wu, C.F. Njeh, S. Zhao, Y. Lu, E. Tsuda-Futami, T. Fuerst, H.K. Genant, Assessment of a new quantitative ultrasound calcaneus measurement: precision and discrimination of hip fractures in elderly women compared with dual X-ray absorptiometry, Osteoporos. Int. 11 (2000) 354–360, https://doi.org/10.1007/s001980070125.
[30] R.W. Jakes, K. Khaw, N.E. Day, S. Bingham, A. Welch, S. Oakes, R. Luben, N. Dalzell, J. Reeve, N.J. Wareham, Primary care by heel bone among Norfolk cohort of european population based study, Br. Med. J. 322 (2001) 1–5.
[31] A. Welch, Æ.J. Camus, Æ.N. Dalzell, S. Oakes, Æ.J. Reeve, Broadband ultrasound attenuation (BUA) of the heel bone and its correlates in men and women in the EPIC-Norfolk cohort : a cross-sectional population-based study, Osteoporos. Int. 15 (2004) 217–225, https://doi.org/10.1007/s00198-003-1410-7.
[32] M.B. Dobbs, J. Buckwalter, C. Saltzman, Osteoporosis: the increasing role of the orthopaedist, Iowa Orthop. J. 19 (1999) 43–52.
[33] G.V. Ostir, K.S. Markides, S.A. Black, J.S. Goodwin, Lower body functioning as a predictor of subsequent disability among older Mexican Americans, J. Gerontol. Ser. A Biol. Med. Sci. 53 (1998) 491–495, https://doi.org/10.1093/gerona/53A.6.M491.
[34] T. Furuna, H. Nagasaki, S. Nishizawa, M. Sugiura, H. Ukuzumi, H. Ito, T. Kinugasa, K. Hashizume, H. Maruyama, Longitudinal change in the physical performance of older adults in the community, J. Japanese Phys. Ther. Assoc. 1 (1998) 1–5, https://doi.org/10.1298/jjpta.1.1.
[35] R. Lohman, T. Roche, A. Martorell, Anthropometric Standardization Reference Manual, Human Kinetics Books, Champaign, IL, 1991.
[36] N.J. Wareham, R.W. Jakes, K.L. Rennie, J. Schuit, J. Mitchell, S. Hennings, N. E. Day, Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the european prospective investigation into cancer and nutrition (EPIC) study, Public Health Nutr. 6 (2003) 407–413, https://doi.org/10.1079/phn2002439.
[37] Y. Du, L.J. Zhao, Q. Xu, K.H. Wu, H.W. Deng, Socioeconomic status and bone mineral density in adults by race/ethnicity and gender: the Louisiana osteoporosis study, Osteoporos. Int. 28 (2017) 1699–1709, https://doi.org/10.1007/s00198-017-3951-1.
[38] S.L. Brennan, T.M. Winzenberg, J.A. Pasco, A.E. Wluka, A.G. Dobbins, G. Jones, Social disadvantage, bone mineral density and vertebral wedge deformities in the tasmanian older adult cohort, Osteoporos. Int. 24 (2013) 1909–1916, https://doi.org/10.1007/s00198-012-2211-7.
[39] H. Jordan, P. Roderick, D. Martin, The index of multiple deprivation 2000 and accessibility effects on health, J. Epidemiol. Community Health 58 (2004) 250–257, https://doi.org/10.1136/jech.2003.013011.
[40] S. Perrott, K. Martin, V.L. Keevil, N.J. Wareham, K.-T. Khaw, P.K. Myint, Self-reported physical functional health predicts future bone mineral density in EPIC-Norfolk cohort, Arch. Osteoporos. 17 (2022) 1–9, https://doi.org/10.1007/s11657-021-01043-z.

[41] H. Syddall, M. Evandrou, C. Cooper, A. Aihie Sayer, Social inequalities in grip strength, physical function, and falls among community dwelling older men and women: findings from the hertfordshire cohort study, J. Aging Health 21 (2009) 913–939, https://doi.org/10.1177/0898264309340793.
[42] T. Sözen, L. Özışık, N.Ç. Başaran, An overview and management of osteoporosis, Eur. J. Rheumatol. 4 (2017) 46–56, https://doi.org/10.5152/eurjrheum.2016.048.
[43] W.M. Hopman, C. Berger, L. Joseph, S.N. Morin, T. Towheed, T. Anastassiades, J. D. Adachi, D.A. Hanley, J.C. Prior, D. Goltzman, Longitudinal assessment of health-related quality of life in osteoporosis: data from the population-based Canadian multicentre osteoporosis study, Osteoporos. Int. 30 (2019) 1635–1644, https://doi.org/10.1007/s00198-019-05000-y.
[44] M. Gambacciani, M. Levancini, Hormone replacement therapy and the prevention of postmenopausal osteoporosis, Prz. Menopauzalny = Menopause Rev. 13 (2014) 213–220, https://doi.org/10.5114/pm.2014.44996.
[45] J.F. Husak, D.J. Irschick, Steroid use and human performance: lessons for integrative biologists, Integr. Comp. Biol. 49 (2009) 354–364, https://doi.org/10.1093/icb/icp015.
[46] K.E. Ensrud, S.K. Ewing, P.M. Cawthon, H.A. Fink, B.C. Taylor, J.A. Cauley, T.-T. Dam, L.M. Marshall, E.S. Orwoll, S.R. Cummings, O.F. in M.R. Group, A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men, J. Am. Geriatr. Soc. 57 (2009) 492–498, https://doi.org/10.1111/j.1532-5415.2009.02137.x.
[47] K.E. Ensrud, S.K. Ewing, B.C. Taylor, H.A. Fink, P.M. Cawthon, K.L. Stone, T. A. Hillier, J.A. Cauley, M.C. Hochberg, N. Rodondi, J.K. Tracy, S.R. Cummings, Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women, Arch. Intern. Med. 168 (2008) 382–389, https://doi.org/10.1001/archinternmed.2007.113.
[48] T. Alfred, Y. Ben-Shlomo, R. Cooper, R. Hardy, C. Cooper, I.J. Deary, Genetic markers of bone and joint health and physical capability in older adults: the HALCyon programme, Bone 52 (2013) 2013, https://doi.org/10.1016/j.bone.2012.10.004.
[49] A. Ahmeidat, S. Bhattacharya, R.N. Luben, K. Khaw, P.K. Myint, Maturitas long-term effects of gestational diabetes on bone mineral density and fracture risk : analysis of the Norfolk cohort of the european prospective investigation into cancer (EPIC-Norfolk) population-based study, Maturitas 144 (2021) 68–73.
[50] C. Julian, M.A.H. Lentjes, I. Huybrechts, R. Luben, N. Wareham, L.A. Moreno, K. Khaw, Fracture risk in relation to serum 25- hydroxyvitamin D and physical activity : results from the EPIC-Norfolk Cohort, PLoS One (2016) 1–16, https://doi.org/10.1371/journal.pone.0164160.
[51] M.H.-R. Duarte Henriques-Neto, João P. Magalhães, L.B.S. Diana, A. Santos, Fátima Baptista, Physical fitness and bone health in young athletes and nonathletes, Sports Health 12 (2020) 441–448, https://doi.org/10.1177/1941738120931755.
[52] K. Jayne, E.C. Sale, Exercise and bone health across the lifespan, Biogerontology 18 (2017) 931–946, https://doi.org/10.1007/s10522-017-9732-6.
[53] M. Locquet, C. Beaudart, J.-Y. Reginster, O. Bruyère, Association between the decline in muscle health and the decline in bone health in older individuals from the SarcoPhAge cohort, Calcif. Tissue Int. 104 (2019) 273–284, https://doi.org/10.1007/s00223-018-0503-4.
[54] O. Berriche, A. Chiraz, R. Ben Othman, H. Souheila, I. Lahmer, C. Wafa, I. Sebai, H. Sfar, F. Mahjoub, H. Jamoussi, Nutritional risk factors for postmenopausal osteoporosis, Alex. J. Med. 53 (2017) 187–192, https://doi.org/10.1016/j.ajme.2016.03.007.
[55] P.M. Cawthon, L.M. Marshall, Y. Michael, T.T. Dam, K.E. Ensrud, E. Barrett-Connor, E.S. Orwoll, Frailty in older men: prevalence, progression, and relationship with mortality, J. Am. Geriatr. Soc. 55 (2007) 1216–1223, https://doi.org/10.1111/j.1532-5415.2007.01259.x.
[56] J.S. Finkelstein, S.E. Brockwell, V. Mehta, G.A. Greendale, M.R. Sowers, B. Ettinger, J.C. Lo, J.M. Johnston, J.A. Cauley, M.E. Danielson, R.M. Neer, Bone mineral density changes during the menopause transition in a multiethnic cohort of women, J. Clin. Endocrinol. Metab. 93 (2008) 861–868, https://doi.org/10.1210/jc.2007-1876.
[57] A. Oksuzyan, K. Juel, J.W. Vaupel, K. Christensen, Men: good health and high mortality. Sex differences in health and aging, Aging Clin. Exp. Res. 20 (2008) 91–102, https://doi.org/10.1007/BF03324754.
[58] S.A. Hayat, R. Luben, V.L. Keevil, S. Moore, N. Dalzell, A. Bhaniani, A.P. Khawaja, P. Foster, C. Brayne, N.J. Wareham, K.-T. Khaw, Cohort profile: a prospective cohort study of objective physical and cognitive capability and visual health in an ageing population of men and women in Norfolk (EPIC-Norfolk 3), Int. J. Epidemiol. 43 (2014) 1063–1072, https://doi.org/10.1093/ije/dyt086.