Published in final edited form as:

Calcif Tissue Int. 2010 March ; 86(3): 211–219.

Influence of lifestyle factors on quantitative heel ultrasound measurements in middle-aged and elderly men

Stephen R Pye¹, Vinodh Devakumar¹, Steven Boonen^{2,3}, Herman Borghs³, Dirk Vanderschueren^{3,4}, Judith E Adams⁵, Kate A Ward^{5,6}, Gyorgy Bartfai⁷, Felipe F Casanueva⁸, Joseph D Finn¹, Gianni Forti⁹, Aleksander Giwercman¹⁰, Thang S Han¹¹, Ilpo T Huhtaniemi¹², Krzysztof Kula¹³, Michael EJ Lean¹¹, Neil Pendleton¹⁴, Margus Punab¹⁵, Alan J Silman¹, Frederick CW Wu¹⁶, Terence W O'Neill¹, and EMAS study group[†]

¹ARC Epidemiology Unit, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK ²Leuven University Division of Geriatric Medicine, Katholieke Universiteit Leuven, Leuven, Belgium ³Leuven University Center for Metabolic Bone Diseases, Katholieke Universiteit Leuven, Leuven, Belgium ⁴Department of Andrology and Endocrinology, Katholieke Universiteit Leuven, Leuven, Belgium ⁵Clinical Radiology, Imaging Science and Biomedical Engineering, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK ⁶MRC Human Nutrition Research, Cambridge, UK ⁷Department of Obstetrics, Gynaecology and Andrology, Albert Szent-Gyorgy Medical University, Szeged, Hungary ⁸Department of Medicine, Santiago de Compostela University, Complejo Hospitalario Universitario de Santiago (CHUS); CIBER de Fisiopatología Obesidad y Nutrición (CB06/03), Instituto Salud Carlos III; Santiago de Compostela, Spain ⁹Andrology Unit, Department of Clinical Physiopathology, University of Florence, Florence, Italy ¹⁰Scanian Andrology Centre, Department of Urology, Malmö University Hospital, University of Lund, Sweden ¹¹Department of Human Nutrition, University of Glasgow, Glasgow, Scotland ¹²Department of Reproductive Biology, Imperial College London, Hammersmith Campus, London, UK ¹³Department of Andrology and Reproductive Endocrinology, Medical University of Lodz, Lodz, Poland ¹⁴Clinical Gerontology, The University of Manchester, Manchester Academic Health Science Centre, Hope Hospital, Salford, UK ¹⁵Andrology Unit, United Laboratories of Tartu University Clinics, Tartu, Estonia ¹⁶Department of Endocrinology, The University of Manchester, Manchester Academic Health Science Centre, Manchester Royal Infirmary, Manchester, UK

Abstract

We examined the distribution of quantitative heel ultrasound (QUS) parameters in population samples of European men, and looked at the influence of lifestyle factors on the occurrence of these parameters.

Address for Correspondence / Requests for reprints: Dr Terence W. O'Neill, arc Epidemiology Unit, Oxford Road, The University of Manchester, Manchester, M13 9PT, United Kingdom. Telephone Number: 00 44 161 275 5040 ; Fax: 00 44 161 275 5043
terence.o'neill@manchester.ac.uk

[†]The EMAS Study Group: Florence (Gianni Forti, Luisa Petrone, Antonio Cilotti); Leuven (Dirk Vanderschueren, Steven Boonen, Herman Borghs); Lodz (Krzysztof Kula, Jolanta Slowikowska-Hilczek, Renata Walczak-Jedrzejowska); London (Ilpo Huhtaniemi); Malmö (Aleksander Giwercman); Manchester (Frederick Wu, Alan Silman, Terence O'Neill, Joseph Finn, Philip Steer, Abdelouahid Tajar, David Lee, Stephen Pye); Santiago (Felipe Casanueva, Mary Lage); Szeged (Gyorgy Bartfai, Imre Földesi, Imre Fejes); Tartu (Margus Punab, Paul Korrovitz); Turku (Min Jiang)

Men aged between 40 and 79 years were recruited from eight European centres and invited to attend for an interviewer-assisted questionnaire, assessment of physical performance and quantitative ultrasound (QUS) of the calcaneus (Hologic - SAHARA). The relationships between QUS parameters and lifestyle variables were assessed using linear regression with adjustments for age, centre and weight.

3,258 men, mean age 60.0 years were included in the analysis. A higher PASE score (upper vs lower tertile) was associated with higher BUA (β coefficient = 2.44 dB/Mhz), SOS (β coefficient = 6.83 m/s) and QUI (β coefficient = 3.87). Compared to those who were inactive, those who walked or cycled more than an hour per day had a higher BUA (β coeff = 3.71 dB/Mhz), SOS (β coeff = 6.97 m/s) and QUI (β coeff = 4.50). A longer time to walk 50 feet was linked with lower BUA (β coeff = -0.62 dB/Mhz), SOS (β coeff = -1.06 m/s) and QUI (β coeff = -0.69). Smoking was associated with a reduction in BUA, SOS and QUI. There was a U shaped association with frequency of alcohol consumption.

Modification of lifestyle, including increasing physical activity and stopping smoking may help optimise bone strength and reduce the risk of fracture in middle aged and elderly European men.

Keywords

Epidemiology; Ultrasound; Bone mineral density; Risk factors; Exercise

INTRODUCTION

Quantitative heel ultrasound (QUS) measurements at the heel have been shown to be associated with risk of spine and non spine fracture in men and women [1-9]. The strength of prediction has been reported to be at least as strong as that for bone mineral density (BMD_a) measurements assessed using dual energy x-ray absorptiometry (DXA) and, to be independent of DXA BMD_a. There is evidence that fracture rates in men and women vary across Europe with rates higher in northern than southern Europe [10,11]. Whether or not such geographic variation can be explained by variation in the level of ultrasound parameters in these populations is unknown. Furthermore, compared to data using DXA, relatively less is known about the lifestyle factors which influence heel ultrasound parameters in men. There is some evidence that physical activity and smoking may influence heel ultrasound broadband ultrasound attenuation (BUA) and speed of sound (SOS) in men, however, the findings are not always consistent [12-20]. Such data are important - knowledge of risk factors is the first step in the development of effective population wide strategies to optimise bone health.

The European Male Ageing Study is a multicentre population based study of ageing in men aged 40 to 79 years. We used data from the study to determine the distribution of ultrasound parameters BUA, SOS and the derived quantitative ultrasound index (QUI) across different European populations, and to explore the association between lifestyle factors and these parameters.

METHODS

Subjects

The subjects included in this analysis were recruited for participation in the European Male Ageing Study. Men were recruited from population based sampling frames in 8 centres: Florence (Italy), Leuven (Belgium), Lodz (Poland), Malmo (Sweden), Manchester (UK), Santiago del Compostella (Spain), Szeged (Hungary), Tartu (Estonia). Details regarding recruitment, response rates and assessments have been described previously [21]. Participating centres were selected to provide geographical and socioeconomic diversity within Europe, and facilities to perform epidemiological surveys. Stratified random sampling was performed in each centre with the aim of recruiting one hundred men in each of four 10-year age bands: 40-49 years, 50-59 years, 60-69 years, and 70-79 years. Subjects were invited by letter to complete a postal questionnaire and attend for an interviewer-assisted questionnaire, assessment of physical performance and ultrasound of the heel. Subjects were recontacted usually within 4 weeks if they did not reply following a first letter. Ethical approval for the study was obtained in accordance with local institutional requirements in each centre.

Assessments

The postal questionnaire included questions concerning time spent walking or on a bicycle out of doors each day (response set = none / less than 30 minutes / 30 minutes to 1 hour / more than 1 hour), smoking - both ever and currently, alcohol consumption in the previous year (response set = every day / 5-6 days per week / 3-4 days per week / 1-2 days per week / less than once a week / not at all). There was a question also about prior fracture since the age of 25 years (response set = no / yes / don't know). The main study questionnaire included the physical activity scale for the elderly (PASE) and the SF36 quality of life questionnaire [22, 23]. Subjects were asked also whether they were currently being treated for any of a list of fourteen morbidities: heart conditions, high blood pressure, pituitary disease, testicular disease, chronic bronchitis, asthma, peptic ulcer, epilepsy, diabetes, liver conditions, kidney conditions, prostate disease, adrenal disease, thyroid disease. A number of performance measures were undertaken including the Tinetti assessment of balance and gait which included the time taken to sit to stand five times, and also the time taken to walk 50 feet [24, 25]. In addition, height and weight were measured in a standardised fashion.

Quantitative heel ultrasound

Quantitative ultrasound of the heel was performed using the Sahara Clinical Sonometer (Hologic, Bedford, Massachusetts) using a standardised protocol. Each centre used the same machine model, and each calibrated daily with the physical phantom provided by the manufacturer. Outputs included broadband ultrasound attenuation (BUA) and speed of sound (SOS). In addition, machine derived parameters were quantitative ultrasound index (QUI), a measure of stiffness: $QUI = 0.41(SOS) + 0.41(BUA) - 571$ and estimated heel bone mineral density (eBMD) in g/cm^2 , $eBMD = 0.002592 \times (BUA+SOS) - 3.687$. Quality control (QC) was performed in each centre as per manufacturers instructions. All QC results were sent to Leuven and compiled and checked for stability throughout the study. To establish the short-term precision of the method in this population, duplicate measurements

were performed in 20 randomly selected cohort members in one of the centres (Leuven, Belgium). The *in vivo* coefficient of variations (CV) were 2.8% and 0.3% for BUA and SOS, respectively, and 2.3% and 3.4% for QUI and eBMD, respectively. Repeat measurements (10) were performed on a roving phantom at each of the eight centres. Standardised CVs (SCVs) [26] for within machine variability ranged by centre: for SOS, from 1.0% to 5.6%, and BUA from 0.7% to 2.7%. SCVs for between machine variability were 4.8% for BUA and 9.7% for SOS.

Analysis

Descriptive statistics were used to characterize the distribution of the heel ultrasound parameters (BUA, SOS, QUI and eBMD) by age and centre. In the analysis of risk factors PASE & SF36 physical component score (PCS) were categorized into tertiles. We grouped comorbidities by number (none, one, two or more) though we looked also separately at the more frequent individual comorbidities including heart disease, hypertension, cardiovascular disease, bronchitis, diabetes and prostate disease. Body mass index (BMI) was calculated by dividing weight (Kgs) by height squared (m^2).

Linear regression was used to determine the association between each of the measured ultrasound parameters and also QUI, and the various putative risk factors (including age) with the ultrasound parameters as the dependent variables. The results are expressed as absolute differences (β coefficients) and 95% confidence intervals (CI). Adjustments were made initially for age, weight and centre. A multivariable analysis was then performed with statistical models including all the lifestyle factors that were significantly associated with the QUS parameters, and age, weight and centre. We looked also at the association between prior fracture and the ultrasound parameters. Statistical analysis was performed using STATA version 9.2.

RESULTS

Subjects

A total of 3,258 men with a mean age of 60.0 years (SD=11.0) had QUS measurements performed. There were 772 men aged 40-49 years, 874 aged 50-59 years, 816 aged 60-69 years and 796 over 70 years. The number of men in each centre ranged from 388 to 427. Characteristics of the subjects are shown in Table 1. Mean BMI was 27.6 kg/m^2 (SD=4.0), PASE score 196.2 (SD=91.7) and SF36 physical score 50.0 (SD=8.2). 65% of subjects reported walking or cycling for more than 1/2 hour per day. 70% reported having ever smoked, with 21% reporting that they currently smoke. 56% of the men reported consuming alcohol at least one day per week. 23% reported two or more comorbidities and 26% reported a previous fracture. Mean BUA was 80.2 dB/MHz, SOS 1550.7 m/s, and the derived indices, eBMD 0.542 g/cm^2 and QUI 97.7. Characteristics of the subjects by centre are shown in Table 2. There were significant differences in weight, PASE score, SF36 physical score, time taken to go from a sitting to a standing position, time taken to walk 50 feet, time spent walking / cycling, smoking status, alcohol consumption, number of comorbidities and self reported previous fracture by centre.

Associations with age, centre and previous fracture

There were significant differences in the measured parameters BUA and SOS and the derived parameter QUI by centre, see Table 3. BUA was lowest in Szeged, Hungary and highest in Manchester, UK (70.4dB/MHz vs 87.7dB/MHz), as was QUI (90.4 vs 104.9). SOS values were lowest in Florence, Italy and highest in Leuven, Belgium (1542.5m/s vs 1561.2m/s). There was no evidence of any consistent geographic trend towards higher or lower levels in northwestern (Leuven, Malmo, Manchester), southern (Florence, Santiago) or eastern Europe (Lodz, Tartu, Szeged). The variation by centre was similar in those aged above and below 65 years. There was an apparent decline in BUA, SOS and QUI with age, see Figures 1-3, though given the cross-sectional nature of the data this needs to be interpreted with some caution. There was no evidence of any significant age centre interaction for BUA (p value= 0.49), SOS (p value= 0.24) or QUI (p value = 0.33). After adjustment for age, an increase in weight was significantly associated with an increase in all three QUS parameters: BUA (β coefficient=0.21 dB/MHz), SOS (β coefficient=0.17 m/s) and QUI (β coefficient=0.16). Significant centre differences in the ultrasound parameters persisted after adjustment for age, weight and also number and type of comorbidities. Also after further adjustment for frequency of alcohol intake, smoking and physical activity. After adjustment for age, weight and centre, compared to those without, those with a history of self reported fracture since age 25 years had significantly lower ultrasound values: BUA (β coefficient= -5.4 dB/MHz), SOS (β coefficient= -10.4 m/s) and QUI (β coefficient= -6.5).

Association with lifestyle factors

The association between SOS, BUA and QUI and lifestyle factors is shown in Table 4. The major finding was that increasing levels of physical activity were associated with an increase in all three QUS parameters. After adjustment for age, weight and centre, compared to those in the lowest tertile of PASE score, those in the upper tertile had an increased BUA (β coefficient= 2.44 dB/MHz), SOS (β coefficient=6.83 m/s) and QUI (β coefficient=3.87). Similarly, compared to those who did no walking or cycling, those that walked or cycled for more than 1 hour per day had an increased BUA (β coefficient=3.71 dB/MHz), SOS (β coefficient=6.97 m/s) and QUI (β coefficient=4.50). A longer time taken to perform sitting to standing (five times) was associated with a reduced BUA (β coefficient = -0.19 dB/MHz), SOS (β coefficient= -0.53 m/s) and QUI (β coefficient= -0.29), as was a longer time taken to walk 50 feet (β coefficient = -0.62 dB/MHz, -1.06 m/s and -0.69 for BUA, SOS and QUI respectively). Compared to those in the lowest tertile of SF36 physical component score, those in the upper tertile had an increased BUA (β coefficient= 2.80 dB/MHz), SOS (β coefficient=5.75 m/s) and QUI (β coefficient=3.44). Further adjustment for individual comorbid conditions (heart disease, hypertension, cardiovascular disease, bronchitis, diabetes, prostate disease) or by number of comorbidities did not attenuate the association between QUS parameters and the physical activity measures suggesting the association is not explained by the presence of underlying comorbid disease.

Other lifestyle factors were associated with the ultrasound parameters. After adjustment for age, centre and weight, compared to those that have never smoked, those who ever smoked had a lower BUA (β coefficient=-4.55 dB/MHz), SOS (β coefficient = -10.32 m/s) and QUI (β coefficient= -6.01). Similarly, those who currently smoke had a lower BUA (β coefficient

=−4.96 dB/MHz), SOS (β coefficient= −11.44 m/s) and QUI (β coefficient=−6.57). There was a U shaped association with frequency of alcohol consumption. Compared to those who drank 1-2 times per week, those who did not drink at all had a lower BUA (β coefficient = −3.19 dB/MHz), SOS (β coefficient= −4.92 m/s) and QUI (β coefficient=−3.43). Also, compared to those who drank 1-2 times per week, those who consumed alcohol every day had a lower BUA (β coefficient =−3.73 dB/MHz), SOS (β coefficient= −7.63 m/s) and QUI (β coefficient=−4.73). Further adjustment for individual comorbid conditions (heart disease, hypertension, cardiovascular disease, bronchitis, diabetes, prostate disease) or number of comorbidities did not attenuate the association between QUS parameters and smoking (ever or current) or alcohol consumption.

When all the lifestyle factors that were associated with the ultrasound parameters were included in a multivariable model, BUA remained positively associated with measures of physical activity including time spent walking or cycling and SF36 physical score, and negatively associated with time taken to walk 50 feet, current smoking and alcohol consumption, see Table 5. Similarly, SOS and QUI remained positively associated with PASE score, time spent walking or cycling and SF36 physical score, and negatively associated with time taken to walk 50 feet, current smoking and alcohol consumption.

DISCUSSION

In this population survey, there was evidence of variation in levels of measured heel ultrasound parameters, BUA, SOS and also QUI across Europe. The ultrasound parameters decreased with age with no evidence, however, of any important age centre interaction. Increased levels of physical activity, and physical performance were associated with higher BUA and SOS while smoking was associated with lower values. There was a U shaped association with frequency of alcohol intake.

Our study was population based, and used standardised methods in assessment of QUS and of lifestyle and other characteristics. There are, however, limitations which need to be considered when interpreting the results. The overall response rate for participation was 45%. It is possible that those invited but who did not take part may have differed with respect to levels of the ultrasound parameters. Assessment for possible response bias requires some auxiliary data about non-responders. In EMAS a sample of non-responders was contacted by telephone and invited to complete a short survey. Compared to EMAS participants, those who took part in the telephone survey ($n = 361$) were more likely to be current smokers (33 vs. 21%; $p < 0.001$). No differences were found, however, in general health, time spent walking or cycling per day, or the proportion who had ever smoked [21]. While some caution is needed in interpreting the data, factors influencing participation are unlikely to have influenced the results of the risk factor analysis which was based on an internal comparison of those who participated. Questionnaires and other instruments used in the study were translated from English into the seven European languages in which their use was intended. Given concerns that subtle differences in the translation process may have influenced questionnaire responses, the questionnaire was back-translated by language experts from the relevant European language back into English. Given that the subjects were unaware of their bone ultrasound measurement results, any misclassification related to

questionnaire response is likely, however, to be random and therefore would tend to reduce the likelihood of finding significant biological associations. There are no published methods for cross-calibration of QUS [27] and the results reported are the data as obtained at each centre. Any errors related to measurement, however, are likely to be non-directional and would tend to reduce the risk of finding significant biological associations. Given the cross-sectional design of the study it is not possible to determine the temporal nature of the observed relationships, for which prospective data are needed, although it seems unlikely that lower ultrasound parameters would lead to a reduction in levels of physical activity. Finally, the study was based on assessment of middle aged and elderly European men and extrapolation beyond this group should be undertaken with caution.

In the analyses there was variation in the distribution of the ultrasound parameters across Europe. There was no consistent geographic pattern towards higher or lower levels in northern or southern Europe. There is evidence from epidemiological studies that fracture rates are higher in Scandinavia than elsewhere in Europe [10,11], however, in our study mean BUA and SOS in Malmo, Sweden, were close to the average in these European men. As discussed, however, we did not undertake any cross-calibration and some caution is required in interpreting this data. Our data show a decline in bone ultrasound parameters with age with no evidence of any important centre difference in the rate of decline. Over the four decade span of those who participated, the average annual decline amounted to 0.16% for BUA, 0.03% for SOS and 0.23% for QUI. In an observational study of 1,138 Spanish men aged 18-99, using the same measurement device, the QUS parameters declined by between 0.08 and 0.41% per year [28]. A decrease in the parameters with age has been observed using other sonometers [17,19,29-32].

In our study physical activity was positively associated with the bone ultrasound parameters. The activity measures which we studied, however, primarily assessed the amount or volume of activity rather than loading, which may be more important to bone health. Most, though not all, studies which have examined the impact of physical activity on heel ultrasound parameters in men suggest a beneficial effect [12-20]. In one of the largest studies of 4981 men, aged 60-80 years, recalled physical activity was linked with increased QUI as measured using a Lunar Achilles device [17]. Most studies though have focused on historical or self report of physical activity linked with ultrasound measures. In our study we observed an association also with two physical performance measures, including the time taken to sit and stand five times, and the time to walk 50 feet test; those who took longer to perform these activities having lower ultrasound parameters. It seems likely that these are a proxy for higher levels of physical activity including higher intensity activities and consequent bone loading though we can not confirm or refute this [33]. Also our assessment of bone health was restricted to the heel and it is possible that the effect may differ at other skeletal sites. In women, for example, walking has a greater impact on the calcaneus than the hip and spine [34].

Other lifestyle factors were important in men. Smoking, both ever and current, was linked with a reduction in all ultrasound parameters. Previous studies using both the Sahara device and other sonometers provide somewhat discrepant findings, with some though not all reporting a negative association [12-13,15-17,19,29,32,35]. There are fewer data concerning

the impact of alcohol consumption with most suggesting no association [12,15,17,36–40]. In our study we found a U-shaped association between alcohol consumption and the QUS measures, where compared to moderate drinking, both light and heavy drinking was associated with a reduction in QUS. This is consistent with some data from bone mass measurement studies finding that social drinking is associated with beneficial effects on bone mass [41].

What is the potential impact of our findings in relation to fracture occurrence? QUS parameters have been linked with fracture in previous studies in both men and women [1–9]. In our study a self reported history of fracture was associated with a reduction in BUA, SOS and QUI. Data from a large prospective study showed that the risk of both hip and non hip fracture increased by a factor of two fold for each unit (SD) change in BUA and SOS [5]. In our study the difference in SOS between those who did and did not smoke amounted to an approximate one third of a standard deviation of the measurement, while for the physical activity scores (PASE and SF36 PCS) the difference in SOS between those in the lowest and highest tertiles of activity was about one fifth of a standard deviation. Although the risk of fracture attributable to the different exposures is relatively small, given that they are potentially modifiable and common they would certainly be potential candidates for inclusion in a population strategy for fracture prevention to optimise bone health in middle age and elderly men with the ultimate aim of reducing fracture occurrence. Some caution, however, is needed in interpreting the data in relation to physical activity as physical activity may influence fracture risk by influencing susceptibility to and also risk of falls [33,42].

In this population survey of European men, QUS parameters declined with age and varied by centre across Europe. Lifestyle factors including physical activity, smoking and alcohol intake influenced bone health.

Acknowledgments

The European Male Ageing Study (EMAS) is funded by the Commission of the European Communities Fifth Framework Programme “Quality of Life and Management of Living Resources” Grant QLK6-CT-2001-00258 and supported by funding from the UK Arthritis Research Campaign. For additional information regarding EMAS contact Frederick Wu, MD; Dept of Endocrinology, Manchester Royal Infirmary, UK. The authors wish to thank the men who participated in the eight countries, the research/nursing staff in the eight centres: C Pott, Manchester, E Wouters, Leuven, M Nilsson, Malmö, M del Mar Fernandez, Santiago de Compostela, M Jedrzejowska, Lodz, H-M Tabo, Tartu, A Heredi, Szeged for their data collection and C Moseley, Manchester for data entry and project coordination. Dr. Vanderschueren and Dr. Boonen are senior clinical investigators of the Fund for Scientific Research-Flanders, Belgium (F.W.O.-Vlaanderen). Dr. Boonen is holder of the Leuven University Chair in Metabolic Bone Diseases.

REFERENCES

1. Bauer DC, Ewing SK, Cauley JA, et al. Quantitative ultrasound predicts hip and non-spine fracture in men: the MrOS study. *Osteoporos Int.* 2007; 18:771–7. [PubMed: 17273893]
2. Meszaros S, Toth E, Ferencz V, et al. Calcaneous quantitative ultrasound measurements predicts vertebral fractures in idiopathic male osteoporosis. *Joint Bone Spine.* 2007; 74:79–84. [PubMed: 17197223]
3. Marin F, Gonzalez-Macias J, Diez-Perez A, et al. Relationship between bone quantitative ultrasound and fractures: a meta-analysis. *J Bone Miner Res.* 2006; 21:1126–35. [PubMed: 16813534]

4. Varenna M, Sinigaglia L, Adami S, et al. Association of quantitative heel ultrasound with history of osteoporotic fractures in elderly men: the ESOPO study. *Osteoporos Int.* 2005; 16:1749–54. [PubMed: 15976988]
5. Khaw KT, Reeve J, Luben R, et al. Prediction of total and hip fracture risk in men and women by quantitative ultrasound of the calcaneus: EPIC-Norfolk prospective population study. *Lancet.* 2004; 363:197–202. [PubMed: 14738792]
6. Boonen S, Nicholson P. Assessment of femoral bone fragility and fracture risk by ultrasonic measurements at the calcaneus. *Age Ageing.* 1998; 27:231–7. [PubMed: 16296685]
7. Bauer DC, Gluer CC, Cauley JA, et al. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. A prospective study. Study of Osteoporotic Fractures Research Group. *Arch Intern Med.* 1997; 157:629–34. [PubMed: 9080917]
8. Hans D, Dargent-Molina P, Schott AM, et al. Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. *Lancet.* 1996; 348:511–4. [PubMed: 8757153]
9. Moayyeri A, Kaptoge S, Dalzell N, et al. Is QUS or DXA Better for Predicting The 10-year Absolute Risk of Fracture? *J Bone Miner Res.* 2009; 24:1319–25. [PubMed: 19257820]
10. Johnell O, Gullberg B, Allander E, et al. The apparent incidence of hip fracture in Europe: A study of national register sources. *Osteoporosis Int.* 1992; 2:298–302.
11. O'Neill TW, Varlow J, Felsenberg D, et al. The prevalence of vertebral deformity in European men and women: The European Vertebral Osteoporosis Study. *J Bone Miner Res.* 1996; 11:1010–7. [PubMed: 8797123]
12. Kauppi M, Impivaara O, Maki J, et al. Vitamin D status and common risk factors for bone fragility as determinants of quantitative ultrasound variables in a nationally representative population sample. *Bone.* 2009; 45:119–24. [PubMed: 19328875]
13. Canhao H, Lucas R, Fonseca JE, et al. Factors influencing calcaneus quantitative ultrasound measurements in an urban population. *Clin Exp Rheumatol.* 2008; 26:67–72. [PubMed: 18328149]
14. Daly RM, Bass SL. Lifetime sport and leisure activity participation is associated with greater bone size, quality and strength in older men. *Osteoporos Int.* 2006; 17(8):1258–67. [PubMed: 16680498]
15. Babaroutsi E, Magkos F, Manios Y, et al. Body mass index, calcium intake, and physical activity affect calcaneal ultrasound in healthy Greek males in an age-dependent and parameter-specific manner. *J Bone Miner Metab.* 2005; 23:157–66. [PubMed: 15750695]
16. Kolbe-Alexander TL, Charlton KE, Lambert EV. Lifetime physical activity and determinants of estimated bone mineral density using calcaneal ultrasound in older South African adults. *J Nutr Health Aging.* 2004; 8:521–30. [PubMed: 15543427]
17. Adami S, Giannini S, Giorgino R, et al. The effect of age, weight, and lifestyle factors on calcaneal quantitative ultrasound: the ESOPO study. *Osteoporos Int.* 2003; 14:198–207. [PubMed: 12730794]
18. Jakes RW, Khaw K, Day NE, et al. Patterns of physical activity and ultrasound attenuation by heel bone among Norfolk cohort of European Prospective Investigation of Cancer (EPIC Norfolk): population based study. *BMJ.* 2001; 322:140. [PubMed: 11159572]
19. Landin-Wilhelmsen K, Johansson S, Rosengren A, et al. Calcaneal ultrasound measurements are determined by age and physical activity. Studies in two Swedish random population samples. *J Intern Med.* 2000; 247:269–78. [PubMed: 10692091]
20. Graafmans WC, Bouter LM, Lips P. The influence of physical activity and fractures on ultrasound parameters in elderly people. *Osteoporos Int.* 1998; 8:449–54. [PubMed: 9850353]
21. Lee DM, O'Neill TW, Pye SR, et al. The European Male Ageing Study (EMAS): design, methods and recruitment. *Int J Androl.* 2009; 32:11–24. [PubMed: 18328041]
22. Washburn RA, Smith KW, Jette AM, et al. The Physical Activity Scale for the Elderly (PASE): development and evaluation. *J Clin Epidemiol.* 1993; 46:153–62. [PubMed: 8437031]
23. Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. *BMJ.* 1993; 306:1437–40. [PubMed: 8518639]
24. Tinetti ME, Williams TF, Mayewski R. Fall risk index for elderly patients based on number of chronic disabilities. *Am J Med.* 1986; 80:429–34. [PubMed: 3953620]

25. Reuben DB, Siu AL. An objective measure of physical function of elderly outpatients. The Physical Performance Test. *J Am Geriatr Soc.* 1990; 38:1105–12. [PubMed: 2229864]
26. Glüer CC, Blake G, Lu Y, et al. Accurate assessment of precision errors: how to measure the reproducibility of bone densitometry techniques. *Osteoporos Int.* 1995; 5:262–70. [PubMed: 7492865]
27. Glüer CC, Eastell R, Reid DM, et al. Association of five quantitative ultrasound devices and bone densitometry with osteoporotic vertebral fractures in a population-based sample: the OPUS Study. *J Bone Miner Res.* 2004; 19:782–93. [PubMed: 15068502]
28. Sosa M, Saavedra P, Munoz-Torres M, et al. Quantitative ultrasound calcaneus measurements: normative data and precision in the spanish population. *Osteoporos Int.* 2002; 13:487–92. [PubMed: 12107663]
29. Welch A, Camus J, Dalzell N, et al. 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.* 2004; 15:217–25. [PubMed: 14745486]
30. Cepollaro C, Agnusdei D, Gonnelli S, et al. Ultrasonographic assessment of bone in normal Italian males and females. *Br J Radiol.* 1995; 68:910–4. [PubMed: 7551790]
31. Moris M, Peretz A, Tjeka R, et al. Quantitative ultrasound bone measurements: normal values and comparison with bone mineral density by dual X-ray absorptiometry. *Calcif Tissue Int.* 1995; 57:6–10. [PubMed: 7671166]
32. van Daele PL, Burger H, Algra D, et al. Age-associated changes in ultrasound measurements of the calcaneus in men and women: the Rotterdam Study. *J Bone Miner Res.* 1994; 9:1751–7. [PubMed: 7863827]
33. Kohrt WM, Bloomfield SA, Little KD, et al. Physical activity and bone health. *Med Sci Sports Exerc.* 2004; 36:1985–1996. [PubMed: 15514517]
34. Brooke-Wavell K, Jones PRM, Hardman AE. Brisk walking reduces calcaneal bone loss in post-menopausal women. *Clin Sci.* 1997; 92:75–80. [PubMed: 9038595]
35. Bernaards CM, Twisk JW, Snel J, et al. Smoking and quantitative ultrasound parameters in the calcaneus in 36-year-old men and women. *Osteoporos Int.* 2004; 15:735–41. [PubMed: 14997288]
36. Babaroutsi E, Magkos F, Manios Y, et al. Lifestyle factors affecting heel ultrasound in Greek females across different life stages. *Osteoporos Int.* 2005; 16:552–61. [PubMed: 15688124]
37. Korpelainen R, Korpelainen J, Heikkinen J, et al. Lifestyle factors are associated with osteoporosis in lean women but not in normal and overweight women: a population-based cohort study of 1222 women. *Osteoporos Int.* 2003; 14:34–43. [PubMed: 12577183]
38. Fukuharu M, Sato J, Ohsawa I, et al. Effects of lifestyle factors on ultrasonographically determined bone health in Japanese women. *Public Health.* 2001; 115:146–51. [PubMed: 11406781]
39. Cheng S, Fan B, Wang L, et al. Factors affecting broadband ultrasound attenuation results of the calcaneus using a gel-coupled quantitative ultrasound scanning system. *Osteoporos Int.* 1999; 10:495–504. [PubMed: 10663351]
40. Gregg EW, Kriska AM, Salamone LM, et al. Correlates of quantitative ultrasound in the Women's Healthy Lifestyle Project. *Osteoporos Int.* 1999; 10:416–24. [PubMed: 10591840]
41. Holbrook TL, Barrett-Connor E. A prospective study of alcohol consumption and bone mineral density. *BMJ.* 1993; 306:1506–9. [PubMed: 8518677]
42. O'Neill TW, Marsden D, Adams JE, et al. Risk factors, falls, and fracture of the distal forearm in Manchester, UK. *J Epidemiol Community Health.* 1996; 50:288–292. [PubMed: 8935460]

Figure 1. Association between broadband ultrasound attenuation (BUA) and age.

Figure 2. Association between speed of sound (SOS) and age.

Figure 3. Association between quantitative ultrasound index (QUI) and age.

Table 1**Subject characteristics.**

Variable	N=3,258
	Mean (SD)
Age at interview (years)	60.0 (11.0)
Height (cm)	173.6 (7.3)
Weight (kg)	83.3 (13.7)
Body mass index (kg/m ²)	27.6 (4.0)
PASE score (0-1100)	196.2 (91.7)
SF36 Physical score (0-100)	50.0 (8.2)
Tinetti: time taken from sitting to standing (s)	12.7 (4.2)
PPT: time taken to walk 50 feet (s)	13.6 (3.4)
Broadband ultrasound attenuation (dB/MHz)	80.2 (19.0)
Speed of sound (m/s)	1550.7 (34.1)
Bone mineral density (g/cm ²)	0.542 (0.137)
Quantitative ultrasound index	97.7 (21.2)
	%
Walking or cycling for ½ hour or more / day	65.3
Ever smoked (yes vs no)	70.1
Currently smoke (yes vs no)	21.0
Alcohol consumption 1day / week	56.2
Comorbidities: None	49.8
One	27.7
Two or more	22.6
Previous fracture since 25 (yes vs no)	25.9

Table 2

Subject characteristics by centre.

	Overall	North/West			East			South		P value ^a
		Leuven	Malmo	Manchester	Lodz	Szeged	Tartu	Florence	Santiago	
Weight (kg)	83.3 (13.7)	82.1 (13.0)	85.4 (13.2)	84.1 (13.3)	82.1 (12.8)	86.5 (14.2)	87.2 (16.2)	79.7 (13.3)	79.8 (11.5)	<0.001
PASE score (0-1100)	196.2 (91.7)	191.7 (86.7)	180.3 (80.1)	219.6 (84.0)	181.5 (93.6)	252.6 (96.2)	204.0 (84.8)	155.3 (76.3)	184.0 (95.6)	<0.001
SF36 Physical score (0-100)	50.0 (8.2)	50.0 (7.9)	51.8 (7.7)	51.2 (7.6)	47.9 (8.3)	49.8 (8.4)	45.6 (9.7)	52.6 (6.1)	51.3 (6.9)	<0.001
Tinetti: time taken from sitting to standing (s)	12.7 (4.2)	12.9 (3.3)	13.4 (5.8)	12.0 (3.2)	12.9 (6.1)	11.7 (3.2)	13.5 (4.0)	10.7 (2.6)	14.4 (3.1)	<0.001
PPT: time taken to walk 50 feet (s)	13.6 (3.4)	13.7 (2.3)	13.4 (3.1)	13.9 (3.0)	14.2 (3.4)	13.8 (3.3)	14.6 (3.9)	10.5 (1.9)	14.7 (3.8)	<0.001
					%					
Walking or cycling for ½ hour or more / day	65.3	47.7	78.9	65.1	70.9	76.1	63.7	54.1	67.6	<0.001
Ever smoked (yes vs no)	70.1	64.4	68.8	56.6	82.1	64.9	74.5	77.1	72.5	<0.001
Currently smoke (yes vs no)	21.0	17.2	16.5	11.4	25.7	21.3	29.2	23.1	23.0	<0.001
Alcohol consumption 1day/week	56.2	73.3	64.7	76.7	23.7	56.7	31.3	54.3	68.0	<0.001
At least one comorbidity	50.3	46.1	38.6	39.0	66.7	58.9	48.7	50.5	52.9	<0.001
Previous fracture since 25 (yes vs no)	25.9	22.6	21.3	25.0	26.6	30.6	35.8	22.7	22.5	<0.001

22

^aTest for differences between centres. ANOVA for continuous, chi-squared test for dichotomous measures

Table 3
Quantitative ultrasound parameters by centre.

Region	Centre	n	Broadband Attenuation (dB/MHz) mean (SD)	Speed of Sound (m/s) mean (SD)	Quantitative Ultrasound Index mean (SD)
North/West	Leuven	424	82.4 (18.3)	1561.2 (32.9)	102.9 (20.5)
	Malmo	389	81.4 (16.4)	1549.3 (29.8)	97.5 (18.2)
	Manchester	388	87.7 (17.1)	1560.8 (34.5)	104.9 (20.6)
East	Lodz	403	79.9 (18.4)	1547.1 (32.6)	96.1 (20.3)
	Szeged	425	70.4 (19.0)	1542.7 (30.1)	90.4 (19.7)
	Tartu	397	79.3 (17.9)	1544.5 (33.6)	94.8 (20.7)
South	Florence	427	77.0 (17.6)	1542.5 (32.6)	93.0 (20.0)
	Santiago	405	84.1 (21.5)	1557.7 (39.5)	102.3 (24.5)

Table 4
Influence of lifestyle factors on ultrasound parameters (with adjustments for age, centre and weight).

	Broadband Attenuation (dB/Mhz)	Speed of Sound (m/s)	Quantitative Ultrasound Index
	β co-efficient ^I (95% CI)	β co-efficient ^I (95% CI)	β co-efficient ^I (95% CI)
Ever smoked (yes vs no)	-4.551 (-5.923, -3.179)*	-10.319 (-12.811, -7.826)*	-6.007 (-7.553, -4.461)*
Current smoker (yes vs no)	-4.959 (-6.517, -3.401)*	-11.444 (-14.277, -8.611)*	-6.565 (-8.322, -4.809)*
Alcohol consumption (days/week)			
None	-3.186 (-5.292, -1.081)*	-4.923 (-8.770, -1.076)*	-3.427 (-5.809, -1.046)*
< 1	-0.950 (-2.798, 0.898)	-2.029 (-5.406, 1.348)	-1.337 (-3.427, 0.753)
1-2	Referent	Referent	Referent
3-4	-2.318 (-4.545, -0.091)*	-4.705 (-8.774, -0.635)*	-2.976 (-5.495, -0.457)*
5-6	-2.870 (-5.600, -0.140)*	-5.383 (-10.371, -0.395)*	-3.469 (-6.557, -0.382)*
Every day	-3.730 (-5.876, -1.584)*	-7.631 (-11.551, -3.710)*	-4.733 (-7.159, -2.306)*
PASE score per 100 (0-1100)	1.547 (0.727, 2.366)*	3.727 (2.237, 5.218)*	2.197 (1.273, 3.121)*
PASE score: tertiles			
Lower	Referent	Referent	Referent
Mid	1.983 (0.326, 3.641)*	4.659 (1.645, 7.674)*	2.837 (0.968, 4.705)*
Upper	2.442 (0.604, 4.281)*	6.829 (3.484, 10.173)*	3.865 (1.792, 5.938)*
Walking or cycling/day			
None	Referent	Referent	Referent
< ½ hour	3.046 (0.827, 5.264)*	5.298 (1.248, 9.348)*	3.509 (1.002, 6.016)*
½ hour – 1 hour	3.042 (0.946, 5.138)*	5.835 (2.008, 9.662)*	3.850 (1.481, 6.220)*
> 1 hour	3.711 (1.539, 5.883)*	6.972 (3.006, 10.938)*	4.500 (2.045, 6.955)*
Walking or cycling (<1/2 hour vs 1/2 hour)	1.355 (-0.017, 2.727)	2.890 (0.385, 5.395)*	1.856 (0.305, 3.407)*
Tinetti: time taken from sitting to standing (s)	-0.187 (-0.343, -0.030)*	-0.526 (-0.811, -0.241)*	-0.294 (-0.470, -0.117)*
PPT: time taken to walk 50 feet (s)	-0.615 (-0.825, -0.404)*	-1.056 (-1.439, -0.672)*	-0.690 (-0.927, -0.452)*
SF36 physical component score (0-100)	0.261 (0.177, 0.345)*	0.503 (0.350, 0.656)*	0.312 (0.218, 0.407)*
SF36 physical component score: tertiles			
Lower	Referent	Referent	Referent
Mid	2.995 (1.407, 4.584)*	5.300 (2.409, 8.191)*	3.435 (1.643, 5.227)*
Upper	2.796 (1.139, 4.452)*	5.754 (2.739, 8.769)*	3.440 (1.571, 5.309)*

* p<0.05

^I adjusted for age, centre and weight

Table 5
Influence of lifestyle factors on ultrasound parameters (with adjustments for age, centre, weight, and other lifestyle variables in model).

	Broadband Attenuation (dB/Mhz)	Speed of Sound (m/s)	Quantitative Ultrasound Index
	β co-efficient ^I (95% CI)	β co-efficient ^I (95% CI)	β co-efficient ^I (95% CI)
Current smoker (yes vs no)	-4.613 (-6.255, -2.971)*	-10.399 (-13.372, -7.426)*	-5.974 (-7.819, -4.130)*
Alcohol consumption (days / week)			
None	-2.105 (-4.303, 0.094)	-2.621 (-6.601, 1.359)	-2.043 (-4.512, 0.426)
< 1	-0.059 (-1.988, 1.869)	-0.537 (-4.029, 2.954)	-0.338 (-2.504, 1.828)
1-2	Referent	Referent	Referent
3-4	-2.034 (-4.328, 0.260)	-4.551 (-8.704, -0.397)*	-2.836 (-5.413, -0.260)*
5-6	-2.219 (-5.045, 0.606)	-4.387 (-9.504, 0.729)	-2.819 (-5.993, 0.355)
Every day	-3.162 (-5.386, -0.937)*	-6.265 (-10.293, -2.238)*	-3.955 (-6.454, -1.456)*
PASE score per 100 (0-1100)	0.692 (-0.174, 1.557)	2.066 (0.499, 3.633)*	1.176 (0.204, 2.148)*
Walking or cycling / day			
None	Referent	Referent	Referent
<1/2 hour	2.549 (0.245, 4.853)*	4.690 (0.519, 8.861)*	3.082 (0.495, 5.670)*
1/2 hour – 1 hour	2.101 (-0.092, 4.293)	3.698 (-0.272, 7.668)	2.612 (0.149, 5.075)*
> 1 hour	2.123 (-0.173, 4.419)	3.490 (-0.667, 7.648)	2.467 (-0.112, 5.046)
Tinetti: time taken from sitting to standing (s)	0.039 (-0.132, 0.210)	-0.121 (-0.430, 0.189)	-0.037 (-0.229, 0.155)
PPT: time taken to walk 50 feet (s)	-0.608 (-0.878, -0.337)*	-0.832 (-1.322, -0.343)*	-0.596 (-0.900, -0.293)*
SF36 physical component score (0-100)	0.173 (0.078, 0.268)*	0.343 (0.171, 0.515)*	0.208 (0.101, 0.315)*

* p<0.05

^I adjusted for age, centre, weight, and other lifestyle variables in model