

# 

**Citation:** Mikkilä S, Johansson J, Nordström A, Nordström P, Emaus N, Handegård BH, et al. (2022) A 15-year follow-up study of hip bone mineral density and associations with leisure time physical activity. The Tromsø Study 2001–2016. PLoS ONE 17(1): e0262228. https://doi.org/ 10.1371/journal.pone.0262228

Editor: Robert Daniel Blank, Medical College of Wisconsin, UNITED STATES

Received: September 1, 2021

Accepted: December 19, 2021

Published: January 26, 2022

**Peer Review History:** PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0262228

**Copyright:** © 2022 Mikkilä et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** The legal restriction on data availability are set by the Tromsø Study Data and Publication Committee in order to control **RESEARCH ARTICLE** 

# A 15-year follow-up study of hip bone mineral density and associations with leisure time physical activity. The Tromsø Study 2001–2016

Saija Mikkilä<sup>1,2</sup>\*, Jonas Johansson<sup>2</sup>, Anna Nordström<sup>1,3</sup>, Peter Nordström<sup>4</sup>, Nina Emaus<sup>5</sup>, Bjørn Helge Handegård<sup>6</sup>, Bente Morseth<sup>1</sup>, Boye Welde<sup>1</sup>

1 School of Sport Sciences, UiT The Arctic University of Norway, Tromsø, Norway, 2 Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway, 3 Department of Public Health and Clinical Medicine, Section for Sustainable Health, Umeå University, Umeå, Sweden, 4 Department of Community Medicine and Rehabilitation, Geriatric Medicine, Umeå University, Umeå, Sweden, 5 Department of Health and Care Sciences, UiT The Arctic University of Norway, Tromsø, Norway, 6 The Regional Centre for Child and Adolescent Mental Health–North, UiT The Arctic University of Norway, Tromsø, Norway, Tromsø, Norway

\* saija.p.mikkila@uit.no

# Abstract

# Aims

The aim was to investigate the long-term association between leisure time physical activity and hip areal bone mineral density (aBMD), in addition to change in hip aBMD over time, in 32–86 years old women and men.

# Methods

Data were retrieved from the 2001, 2007–2008, and 2015–2016 surveys of the Tromsø Study, a longitudinal population study in Norway. Leisure time physical activity was assessed by the four-level Saltin-Grimby Physical Activity Level Scale which refers to physical exertion in the past twelve months. Hip aBMD was assessed by Dual-Energy X-ray Absorptiometry. Linear Mixed Model analysis was used to examine long-term associations between physical activity and hip aBMD (n = 6324). In addition, the annual change in hip aBMD was analyzed in a subsample of 3199 participants.

# Results

Physical activity was significantly and positively associated with total hip aBMD in the overall cohort (p<0.005). Participants who reported vigorous activity had 28.20 mg/cm<sup>2</sup> higher aBMD than those who were inactive (95% CI 14.71; 41.69, controlled for confounders), and even light physical activity was associated with higher aBMD than inactivity (8.32 mg/cm<sup>2</sup>, 95% CI 4.89; 11.76). Associations between physical activity and femoral neck aBMD yielded similar results. Hip aBMD decreased with age in both sexes, although more prominently in women. From 2001 to 2007–2008, aBMD changed by –5.76 mg/cm<sup>2</sup> per year (95% CI – 6.08; –5.44) in women, and –2.31 mg/cm<sup>2</sup> (95% CI –2.69; –1.93), in men. From 2007–2008 to 2015–2016, the change was –4.45 mg/cm<sup>2</sup> per year (95% CI –4.84; –4.06) in women, and –1.45 mg/cm<sup>2</sup> (95% CI –1.92; –0.98) in men.

for data sharing, including publication of datasets with the potential of reverse identification of deidentified sensitive participant information. The data can however be made available from the Tromsø Study upon application to the Tromsø Study Data and Publication Committee. Contact information: The Tromsø Study, Department of Community Medicine, Faculty of Health Sciences, UiT The Arctic University of Norway; e-mail: tromsous@uit.no.

**Funding:** SM's work was funded by Norwegian Women's Public Health Association (<u>https://</u> <u>sanitetskvinnene.no/english</u>). The publication charges for this article have been funded by a grant from the publication fund of UIT The Arctic University of Norway. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing interests:** The authors have declared that no competing interests exist.

# Conclusions

In this cohort of adult men and women, physical activity levels were positively associated with hip aBMD in a dose-response relationship. Hip aBMD decreased with age, although more pronounced in women than men.

# Introduction

Osteoporosis is characterized by reduced bone mineral density (BMD) and poses a worldwide health threat to ageing populations, mainly by increasing the risk of low impact fractures [1]. BMD is a strong predictor of hip fractures, considered to be the most severe among fragility fractures, as they lead to higher morbidity and 14–58% increased mortality risk one year after a hip fracture [2–4]. Furthermore, hip fractures contribute to extensive economic costs in form of hospitalization and rehabilitation [3]. Still, the recovery rate is relatively low compared to other types of fractures [3], and other detrimental health conditions such as walking disabilities are common among hip fracture patients [5,6].

Numerous studies indicate that physical activity improves BMD and thereby reduces the risk of hip fractures [7–9]. However, previous cohort studies on physical activity and BMD have used methodological approaches characterized by small sample sizes, cross-sectional designs, or subpopulations [10–14]. Long-term effects of physical activity on BMD have previously been shown among adults and older adults separately [15–17], although this relationship should be further elucidated across a broad age spectrum in the general population.

The evidence indicating benefits of physical activity on hip BMD could potentially be strengthened by involving large cohort studies, and advanced statistical approaches utilizing longitudinal data. Therefore, the aim of this prospective study was to investigate the association between leisure time physical activity and hip BMD with up to 15 years follow-up in women and men who participated in the population-based Tromsø Study surveys in 2001 (Tromsø5), 2007–2008 (Tromsø6) and 2015–2016 (Tromsø7). In addition, we wanted to examine potential changes in hip BMD with ageing in a large cohort of middle-aged and older adults.

# Methods

# Design, subjects, and ethical approval

The Tromsø Study is a population-based study [18] with repeated surveys conducted in the municipality of Tromsø, Norway. The study was initiated in 1974, and continued with six follow-up surveys in 1979–1980, 1986–1987, 1994–1995, 2001, 2007–2008 and in 2015–2016. All seven surveys include Tromsø municipality residents who were invited to participate through invitation letters. The survey cohorts included total population, birth cohorts and/or random samples of inhabitants in the Tromsø municipality. All participants provided written informed consent prior to inclusion. The Tromsø Study has been approved by the Data Inspectorate of Norway and the Regional Committee of Medical and Health Research Ethics, North Norway (2009/2536, 2010/876 and 2014/940).

This study was based on the Tromsø5, Tromsø6 and Tromsø7 surveys of the Tromsø Study including a total of 7790 participants; 4468 women and 3322 men, aged 32–86 years by the first dual-energy X-ray absorptiometry (DXA) scan. Participants with at least one valid hip areal BMD (aBMD) measurement were included in the prospective follow-up analysis. We



Fig 1. Number and distribution of the participants in the Tromsø Study surveys Tromsø5, Tromsø6 and Tromsø7.

https://doi.org/10.1371/journal.pone.0262228.g001

investigated associations between physical activity and left hip aBMD by using the Tromsø Study data from Tromsø5, Tromsø6 and Tromsø7 in 6324 participants; 3637 women and 2687 men, aged 32–86 years. A total of 9616 observations were included, as each participant could contribute with data on any of the three measuring points; Tromsø5, Tromsø6 and/or Tromsø7. Furthermore, we investigated change in hip BMD in 3199 participants; 1938 women and 1612 men, aged 40–84 years. The total number of scans for the change in the left hip total aBMD was 3947 as participants with at least two consecutive hip aBMD measurements, Tromsø5 and Tromsø6 or/and Tromsø6 and Tromsø7, were included. Fig 1 shows the number of participants and their Tromsø Study survey distribution.

#### Assessment of physical activity

Leisure time physical activity was assessed by the Saltin-Grimby Physical Activity Level Scale (SGPALS) [19], which is a self-administrated multiple-choice question included in a questionnaire on several lifestyle and health-related questions. Questionnaires for the Tromsø5, Tromsø6 and Tromsø7 surveys concerning leisure time exercise and physical exertion accompanied the study invitation. The SGPALS asks about "Exercise and physical exertion in leisure time. If your activity varies much, for example between summer and winter, then give an average. The question refers only to the last twelve months". The participants were asked to choose one of the following response options: 1) Reading, watching TV, or other sedentary activity; 2) Walking, cycling, or other forms of exercise at least 4 hours a week (Including walking or cycling to place of work, Sunday-walking, etc.); 3) Participation in recreational sports, heavy gardening, etc. (Note: duration of activity at least 4 hours a week); 4) Participation in hard training or sports competitions, regularly several times a week. The participants were according to their response option allocated into one of the four levels of physical activity [19].

#### Measurement of bone mineral density

In the Tromsø5, Tromsø6 and Tromsø7 surveys, aBMD was measured by using DXA devices (Lunar Prodigy, GE Medical Systems, Madison, WI, USA) in a randomly selected sub-sample. The first Lunar Prodigy Pro device was used for the Tromsø5 and Tromsø6 measurements, and the second, cross-calibrated with the first device, for Tromsø7. Valid measurements were obtained from 7790 individuals. All scans were performed according to standard procedures set by GE Medical Systems. The DXA device was calibrated daily throughout the surveys using a standard phantom. Trained technicians performed the scanning according to the standard-ized protocol, and one of them performed quality assessment of the total sample afterwards. In a validation study, the short-term in vivo precision error for the Lunar Prodigy was 1.7% and 1.2% for the femoral neck and total hip measurements, respectively [20]. Our main analyses are based on left total hip scans, which include the femoral neck, trochanter and shaft regions [21]. In a sensitivity analysis we included left femoral neck instead of total hip.

#### Additional measurements

Participants' height and weight were measured at the physical examination in light clothing to nearest centimeter and half-kilogram respectively. Body mass index (BMI) was calculated from weight and height (kg/m<sup>2</sup>). Smoking (current, previous or never) was self-reported.

#### Statistical analyses

Descriptive data are presented as means (M) and standard deviations (SD), or as number of participants (N) and percentages (%). Participants with at least two consecutive hip aBMD measurements, Tromsø5 and Tromsø6 or/and Tromsø6 and Tromsø7, were included in the hip aBMD change analysis. Change per year in the left total hip aBMD was studied from Tromsø5 to Tromsø6 and from Tromsø6 to Tromsø7, stratified by 5-year age groups, separately for men and women. From Tromsø5 to Tromsø6, the highest age group 75+, also included subjects above 80 years due to low count of subjects over 75 years at the Tromsø5 baseline. From Tromsø6 to Tromsø7, the highest age group 75+, included subjects < 77 years at the Tromsø6 baseline.

Participants with at least one hip aBMD measurement and data for physical activity, age, BMI, sex and smoking status were included in LMM analysis, and associations between left total hip/femoral neck aBMD and physical activity, adjusted for age, BMI, sex and smoking status were analyzed with an LMM approach. This approach handles the dependency in aBMD observations within individuals, making this a 2-level analysis with observations nested within persons [22]. LMM is analyzed with data in a long format, and therefore handles timevarying independent variables like physical activity. In the LMM, a random intercept and a random slope for age were included in the model. Also, answers for the leisure time physical activity questions were recoded for the linear mixed model analysis: 1->4, 2->3, 3->2, 4->1, and the level 4 (inactive) functioned as a reference group.

We tested interaction terms by involving physical activity first in order to be able to conclude whether the main effect of physical activity level (PA) on the left total hip aBMD should be interpreted. No significant effects of either PA\*sex, PA\*BMI, PA\*age or PA\*smoking were found. We included a sex\*age interaction term in all models tested. Since we have a large sample, an alpha level of 0.005 was chosen for testing the whole sample [23]. 95% confidence intervals were computed when estimating parameters within subgroups of the sample. SPSS version 26 (IBM Corp, Armonk, NY, USA) was used for all analyses.

#### Results

#### Sample characteristics

Table 1 displays sample characteristics stratified by the participants' first Tromsø Study survey examination, for women and men separately. The table presents all 7790 participants with at least one aBMD measurement. Women had a mean age of  $63.1 \pm 9.2$  years and a BMI of  $26.7 \pm 4.6$  kg/m<sup>2</sup>, while corresponding values for men were  $63.9 \pm 9.2$  years and  $27.1 \pm 3.6$  kg/m<sup>2</sup>.

# Physical activity and left hip aBMD

Table 2 shows long-term associations between leisure time physical activity and total hip aBMD, adjusted for sex, age, sex\*age, BMI and smoking habits, in women and men who participated in the population-based Tromsø Study surveys in Tromsø5, Tromsø6 and Tromsø7. Physical activity was significantly and positively associated with left total hip aBMD in the overall cohort ( $F_{3, 3424.8} = 14.38$ ; p < 0.005). Compared with the most inactive participants, aBMD increased gradually with increasing physical activity level, and participants who reported vigorous activity had 28.20mg/cm<sup>2</sup> higher aBMD than those who were inactive ( $t_{3666.9} = 4.10$ ; p < 0.005) (95% CI 14.71; 41.69). Associations between physical activity and femoral neck aBMD were very similar, and the correlation coefficient between total hip aBMD and femoral neck aBMD was approximately 0.90 on all measurement occasions in T5-T7.

# Changes in left total hip aBMD

Changes in aBMD from Tromsø5 to Tromsø6 (women: n = 1419; men: n = 992) stratified by 5-year age groups are shown in Table 3. From Tromsø5 to Tromsø6, the change per year in aBMD was smallest at the age of 40–44 years (-2.84 mg/cm<sup>2</sup>) in women. From the age of 45, the magnitude of the annual change was markedly larger, ranging from -4.87 to -7.81 mg/ cm<sup>2</sup>. In men, aBMD changed progressively and significantly from 55–59 years and up, with a markedly higher decrease in the oldest ( $\geq$  75 years) group compared to younger participants. Overall, the annual aBMD change was -5.76 mg/cm<sup>2</sup> (95% CI -6.08; -5.44) in women, and -2.31 mg/cm<sup>2</sup> (95% CI -2.69; -1.93) in men.

Changes in aBMD from Tromsø6 to Tromsø7 (women: n = 907; men: n = 629) stratified by 5-year age group are shown in Table 4. In women, the patterns in aBMD decrease were similar to the patterns observed between Tromsø5 and Tromsø6. In men, the aBMD started decreasing significantly from 65–69 years, as opposed to ages 55–59 from Tromsø5 to Tromsø6. The aBMD loss was markedly higher in the oldest ( $\geq 75$  years) age groups (-6.41 mg/cm<sup>2</sup>). Mean annual aBMD change was -4.45 mg/cm<sup>2</sup> (95% CI -4.84; -4.06) in women, and -1.45 mg/cm<sup>2</sup> (95% CI -1.92; -0.98) in men.

# Discussion

In this 15-year longitudinal study of adult and elderly women and men, physical activity was positively and linearly associated with hip aBMD. Moreover, the annual decrease in aBMD was rather stable from the age of 45 years in women and from the age of 55–65 years in men.

Women	T5	T6	T7	T6, T7	T5, T6	T5, T7	T5, T6, T7	Total
Age (years)								
n	1221	200	1079	259	967	30	712	4468
M (SD)	67.9 (9.5)	59.3 (7.3)	62.0 (7.9)	57.1 (5.1)	64.7 (8.5)	55.1 (6.7)	58.2 (8.0)	63.1 (9.2)
BMI (kg/m <sup>2</sup> )								
n	1216	200	1078	259	962	30	710	4455
M (SD)	26.9 (4.7)	26.4 (4.8)	26.7 (4.8)	26.3 (4.2)	27.1 (4.5)	25.4 (3.9)	26.4 (4.2)	26.7 (4.6)
Smoking n (%)	1209 (27.3)	199 (4.5)	1063 (24.0)	255 (5.8)	30 (0.7)	961 (21.7)	706 (16.0)	4423 (100.0)
Yes, now	348 (28.8)	58 (29.1)	139 (13.1)	44 (17.3)	7 (23.3)	237 (24.7)	176 (24.9)	1009 (22.8)
Never	532 (44.0)	59 (29.6)	412 (38.8)	81 (31.8)	11 (36.7)	432 (45.0)	294 (41.6)	1821 (41.2)
Yes, previously	329 (27.2)	82 (41.2)	512 (48.2)	130 (51.0)	12 (40.0)	292 (30.4)	236 (33.4)	1593 (36.0)
Hip aBMD (mg/cm <sup>2</sup> )								
n	1221	200	1079	259	967	30	712	4468
M (SD)	869 (142)	921 (145)	928 (136)	940 (115)	911 (136)	920 (109)	946 (125)	911 (138)
Physical activity* n (%)	556 (16.8)	179 (5.4)	1046 (31.6)	240 (7.2)	607 (18.3)	28 (0.8)	656 (19.8)	3312 (100.0)
Inactive (Level 1)	105 (18.9)	38 (21.2)	103 (9.8)	40 (16.7)	103 (17.0)	4 (14.3)	100 (15.2)	493 (14.9)
Light activity (Level 2)	392 (70.5)	119 (66.5)	743 (71.0)	161 (67.1)	441 (72.7)	22 (78.6)	492 75.0)	2370 (71.6)
Moderate activity (Level 3)	56 (10.1)	21 (11.7)	184 (17.6)	35 (14.6)	59 (9.7)	2 (7.1)	62 (9.5)	419 (12.7)
Vigorous activity (Level 4)	3 (0.5)	1 (0.6)	16 (1.5)	4 (1.7)	4 (0.7)	0 (0.0)	2 (0.3)	30 (0.9)
Men	T5	T6	T7	T6, T7	T5, T6	T5, T7	T5, T6, T7	Total
Age (years)								
n	936	213	891	201	655	21	405	3322
M (SD)	68.8 (9.0)	58.8 (7.0)	62.1 (8.4)	58.8 (5.6)	65.7 (8.6)	55.4 (7.9)	59.0 (8.1)	63.9 (9.2)
BMI (kg/m <sup>2</sup> )								
n	928	213	891	201	654	21	404	3312
M (SD)	26.5 (3.5)	27.5 (3.9)	27.7 (4.0)	27.8 (3.7)	27.0 (3.2)	26.9 (1.8)	26.9 (3.0)	27.1 (3.6)
Smoking n (%)	932 (28.6)	209 (6.4)	842 (25.8)	199 (6.1)	652 (20.0)	21 (0.6)	403 (12.4)	3258 (100.0)
Yes, now	272 (29.2)	49 (23.4)	91 (10.8)	21 (10.6)	154 (23.6)	2 (9.5)	88 (21.8)	677 (20.8)
Never	158 (17.0)	65 (31.1)	306 (36.3)	74 (37.2)	127 (19.5)	10 (47.6)	119 (29.5)	859 (26.4)
Yes, previously	502 (53.9)	95 (45.5)	445 (52.9)	104 (52.3)	371 (56.9)	9 (42.9)	196 (48.6)	1722 (52.9)
Hip aBMD (mg/cm <sup>2</sup> )								
n	936	213	891	201	655	21	405	3322
M (SD)	997 (148)	1027 (142)	1061 (155)	1035 (143)	1022 (134)	1089 (94)	1045 (125)	1030 (146)
Physical activity* n (%)	417 (16.8)	195 (7.9)	871 (35.1)	196 (7.9)	400 (16.1)	21 (0.8)	379 (15.3)	2479 (100.0)
Inactive (Level 1)	88 (21.1)	51 (26.2)	113 (13.0)	34 (17.3)	76 (19.0)	3 (14.3)	61 (16.1)	426 (17.2)
Light activity (Level 2)	256 (61.4)	103 (52.8)	480 (55.1)	110 (56.1)	256 (64.0)	13 (61.9)	241 (63.3)	1459 (58.9)
Moderate activity (Level 3)	69 (16.5)	38 (19.5)	260 (29.9)	50 (25.5)	63 (15.8)	5 (23.8)	72 (19.0)	557 (22.5)
Vigorous activity (Level 4)	4 (1.0)	3 (1.5)	18 (2.1)	2 (1.0)	5 (1.3)	0 (0.0)	5 (1.3)	37 (1.5)

Table 1. Sample characteristics stratified by sex and survey participation.

\*Physical activity level 1 = answer alternative 1 (lowest physical activity level); level 4 = answer alternative 4 (highest physical activity level). Survey participation is highlighted in bold dark font, and characteristics are presented at baseline if several surveys were attended. T5: the fifth Tromsø Study in 2001, T6: the sixth Tromsø Study in 2007–2008, T7: the seventh Tromsø Study in 2015–2016.

https://doi.org/10.1371/journal.pone.0262228.t001

Physical inactivity is known to be an important risk factor for bone health [7], and positive associations between physical activity and hip BMD in different populations are well documented in cross-sectional studies [10,13,24–26], although such study designs are vulnerable to reverse causation. Similar findings have also been reported from randomized controlled trials [27–29], however these involve different inclusion criteria, and typically investigate specific

	В	95% CI	F/ df		
Physical activity			14.38*/ 3, 3424.8		
Inactive (Level 1)	Reference	Reference			
Light activity (Level 2)	8.32	(4.89, 11.76)			
Moderate activity (Level 3)	13.56	(9.07, 18.05)			
Vigorous activity (Level 4)	28.20	(14.71, 41.69)			
Age (per year, slope for men)	-1.93	(-0.23, -1.63)	1317.8**/ 1, 2495.2		
<b>BMI</b> (per kg/m <sup>2</sup> )	10.54	(9.95, 11.12)	1244.3**/ 1, 7894.5		
Sex <sup>a</sup>			1352.4**/ 1, 5557.3		
Men	Reference	Reference			
Women	-124.26	(-130.88, -117.63)			
Sex*Age <sup>b</sup>			323.9**/ 1, 2367.1		
Men*age	Reference	Reference			
Women*age	-3.62	(-4.01, -3.22)			
Smoking			17.8*/ 2, 5508.9		
Never	Reference	Reference			
Yes, previously	-16.07	(-21.38, -10.77)			
Yes, now	-15.26	(-21.52, -9.01)			

<sup>a</sup> computed at the mean age of 66.1 years.

<sup>b</sup> difference in age slope for women and men.

\*\* p < 0.0005.

https://doi.org/10.1371/journal.pone.0262228.t002

forms of physical activity, such as resistance exercise and high-impact training, which might not be generalizable to the entire population. It is therefore important to further clarify the relationship between habitual physical activity and bone health in the general population using longitudinal study designs.

This study expands a 22-year follow-up study of associations between leisure time physical activity and hip BMD in earlier Tromsø Study cohorts (1979–1980 and 2001–2002) of women and men aged 20–54 years at baseline [17]. Although the subjects were younger at baseline and follow-up, their findings were similar to our study, thus indicating positive associations

Table 5. Change per year in age-stratified left total inp bone inneral density (ing/cin) and percent/ iron irons05 to iron	Table 3.	Change per year in a	ge-stratified left total hij	p bone mineral density	(mg/cm <sup>2</sup> and p	percent) from Tromsø5 to	o Tromsø6
--	----------	----------------------	------------------------------	------------------------	---------------------------	--------------------------	-----------

	Women					Men				
Age group	N	Mean	SD	95% CI	Annual change (%)	N	Mean	SD	95% CI	Annual change (%)
40-44	46	-2.84	7.71	(-4.60, -1.07)	-0.30	18	-0.72	6.30	(-3.54, 2.11)	-0.04
45-49	41	-7.41	7.82	(-9.28, -5.54)	-0.75	30	0.19	3.99	(-2.00, 2.37)	0.02
50-54	54	-7.81	7.25	(-9.43, -6.18)	-0.80	76	-0.71	4.42	(-2.08, 0.66)	-0.07
55-59	368	-6.01	7.14	(-6.63, -5.38)	-0.62	122	-1.62	4.88	(-2.70, -0.53)	-0.17
60-64	413	-5.75	6.24	(-6.34, -5.16)	-0.61	263	-2.16	5.50	(-2.90, -1.42)	-0.22
65–69	249	-4.87	6.27	(-5.62, -4.11)	-0.53	250	-2.59	5.21	(-3.35, -1.84)	-0.26
70-74	163	-6.04	5.55	(-6.98, -5.10)	-0.70	158	-2.72	5.38	(-3.67, -1.77)	-0.29
75+*	85	-6.35	6.78	(-7.65, -5.05)	-0.75	75	-5.16	6.74	(-6.54, -3.77)	-0.53
Total	1419	-5.76	6.62	(-6.08, -5.44)	-0.62	992	-2.31	5.43	(-2.69, -1.93)	-0.24

\* The highest age group 75+ includes subjects > 80 years. Age groups are based on participants' age at T5.

https://doi.org/10.1371/journal.pone.0262228.t003

<sup>\*</sup> p < .005.

	Women					Men				
Age group	N	Mean	SD	95% CI	Annual change (%)	N	Mean	SD	95% CI	Annual change (%)
40-44	23	-2.98	5.59	(-5.39, -0.57)	-0.32	17	1.30	5.94	(-1.75, 4.35)	0.10
45-49	35	-6.29	6.28	(-8.24, -4.33)	-0.66	13	0.61	3.08	(-2.88, 4.10)	0.06
50-54	108	-5.63	6.43	(-6.74, -4.51)	-0.56	75	0.53	5.00	(-0.92, 1.99)	0.05
55-59	122	-4.13	5.78	(-5.18, -3.09)	-0.44	110	-0.73	5.14	(-1.93, 0.47)	-0.07
60-64	237	-3.66	5.85	(-4.41, -2.91)	-0.39	143	-0.48	5.27	(-1.53, 0.57)	-0.05
65-69	247	-4.84	6.47	(-5.57, -4.10)	-0.51	142	-2.09	5.58	(-3.14, -1.03)	-0.22
70-74	107	-3.58	6.34	(-4.70, -2.46)	-0.39	109	-3.76	5.51	(-4.97, -2.56)	-0.37
75+*	28	-6.81	8.00	(-8.99, -4.63)	-0.72	20	-6.41	6.88	(-8.99, -3.82)	-0.65
Total	907	-4.45	6.27	(-4.84, -4.06)	-0.47	629	-1.45	5.60	(-1.92, -0.98)	-0.15

Table 4. Change per year in age-stratified left hip total bone mineral density (mg/cm<sup>2</sup> and percent) from Tromsø6 to Tromsø7.

\* In the highest age group 75+, all subjects are <77 years. Age groups are based on participants' age at Tromsø6.

https://doi.org/10.1371/journal.pone.0262228.t004

between physical activity and BMD across the lifespan. Kemmler et al. [30] found that exercise had favorable effect on hip and lumbar spine BMD in their 16-year follow-up study of early-postmenopausal osteopenic women. Similarly, large cohort studies show that higher intensity of physical activity is associated with higher forearm BMD in premenopausal [31] and post-menopausal [16] women.

Our findings are comparable with the findings of a 27-year follow-up study in men, although comparability is hampered by different measurements sites; whole body and lumbar spine, and participants' young age (13 years) at baseline [32]. In a cross-sectional study, vigor-ous PA showed the strongest positive association with left femoral neck in 70-year-old men and women, whereas no association was found between PA of any intensity and aBMD of the left radius or lumbar spine [14]. Also, the vertical impacts were found to be stronger than other axial directions [14]. Vertical impact from e.g. running or jumping could be more prominently associated with hip BMD than lumbar spine BMD, or require higher intensity to gain the same effect on lumbar spine[14], which has also been confirmed in experimental studies [27–29]. Further, in a 15-year follow-up study bone loss at the hip was associated with long-term PA, whereas no associations of PA and bone loss in lumbar spine were seen in postmeno-pausal women [33].

Our results show that participants reporting vigorous physical activity had on average 28.2 mg/cm<sup>2</sup> higher aBMD in the left total hip compared with inactive participants, after adjusting for multiple confounders, which corresponds to roughly 3% of the sample mean. To put this into context, a recent randomized clinical trial showed a 5.1% increase in total hip BMD after 15 months of pharmaceutical treatment [34]. However, encouraging inactive individuals to become vigorously physically active is challenging, and physical activity is likely not the sole solution to improving or maintaining BMD in the population. However, the abundance of beneficial health effects that stems from becoming more physically active should not be ignored.

The results from this study should be viewed in light of the following limitations. The SGPALS does not provide specific information on impact direction or type of PA that participants engage in [19], which is also important to consider, because activities such as cycling or swimming might not have the same effects on hip BMD as e.g. running. Also, self-reported physical activity is subject to recall bias and social desirability bias. Nevertheless, in a substudy of Tromsø6, Emaus et al. [35] concluded that the SGPALS has acceptable validity against objectively measured physical activity assessed by the ActiGraph accelerometer in 313 healthy

men and women aged 40–44 years. Similarly, in a population-based cohort of 4040 men and women, Sagelv et al. [36] found positive associations between ranking of physical activity using the SGPALS and accelerometry measured physical activity (p<0.001), although the correlations between SGPALS and accelerometry estimates were weak (r = 0.11 to 0.26, p<0.001). No objective physical activity data to support the subjective measurements was accessible from the Tromsø study in 2001 and 2007–2008. Moreover, our analyses did not include potential confounders such as dietary factors, medication affecting bone metabolism or general health status. The most active participants in our study may have adopted a healthier lifestyle in general, which may have influenced our findings of higher bone mass in this segment. For example, previous studies have shown that nonsmoking and a high physical activity level, as well as a high body weight, reduces bone loss in both sexes [37]. Finally, it should be noted that we have not analyzed other BMD sites, as longitudinal data is not available for e.g. spine.

#### Conclusion

In this cohort of adult and elderly women and men, physical activity was positively associated with left total hip aBMD in a dose-response relationship, after controlling for age, sex, BMI and smoking status. Furthermore, our findings suggest that the decrease in left total hip aBMD is more prominent with ageing in women than in men, although found in both sexes.

Future studies on this topic might benefit from combining objectively measured physical activity data, such as accelerometry measured physical activity, with additional information about the nature of the activity from self-reports in order to advance the knowledge in the field of PA and BMD. As physical activity is a complex behavior to measure, and accelerometers have limitations providing information on activities such as swimming, cycling, and weightlift-ing [38], combining methods and developing a more valid questionnaire for measuring bone specific physical activity, would be beneficial in this area of research.

#### Implications

Although physical activity is positively associated with left total hip aBMD, the effect magnitude of self-reported physical activity is lower than the effect magnitude related to age, sex and BMI. The clinical significance of higher aBMD with higher physical activity levels is difficult to estimate as fracture risk depends on several factors. In general, low hip BMD is a strong predictor of hip fractures in men and women [39], and physical activity should be encouraged in order to prevent BMD loss and thereby reduce fracture risk.

# **Author Contributions**

Conceptualization: Saija Mikkilä, Nina Emaus, Bente Morseth.

Formal analysis: Bjørn Helge Handegård.

Funding acquisition: Saija Mikkilä, Bente Morseth.

Investigation: Nina Emaus.

Methodology: Saija Mikkilä, Nina Emaus, Bjørn Helge Handegård, Bente Morseth.

Project administration: Saija Mikkilä, Bente Morseth, Boye Welde.

Resources: Anna Nordström, Peter Nordström, Nina Emaus, Bente Morseth.

Supervision: Nina Emaus, Bente Morseth, Boye Welde.

Validation: Bjørn Helge Handegård.

- Visualization: Saija Mikkilä, Jonas Johansson, Bjørn Helge Handegård, Bente Morseth, Boye Welde.
- Writing original draft: Saija Mikkilä, Jonas Johansson, Bjørn Helge Handegård, Bente Morseth, Boye Welde.
- Writing review & editing: Saija Mikkilä, Jonas Johansson, Anna Nordström, Peter Nordström, Nina Emaus, Bjørn Helge Handegård, Bente Morseth, Boye Welde.

#### References

- 1. Cole ZA, Dennison EM, Cooper C: Osteoporosis epidemiology update. *Curr Rheumatol Rep* 2008, 10 (2):92–96. https://doi.org/10.1007/s11926-008-0017-6 PMID: 18460262
- Marshall D, Johnell O, Wedel H: Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. *BMJ* 1996, 312(7041):1254–1259. https://doi.org/10.1136/bmj. 312.7041.1254 PMID: 8634613
- Cummings SR, Melton LJ: Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002, 359 (9319):1761–1767. https://doi.org/10.1016/S0140-6736(02)08657-9 PMID: 12049882
- Schnell S, Friedman SM, Mendelson DA, Bingham KW, Kates SL: The 1-year mortality of patients treated in a hip fracture program for elders. *Geriatr Orthop Surg Rehabil* 2010, 1(1):6–14. https://doi. org/10.1177/2151458510378105 PMID: 23569656
- 5. Johnell O, Kanis J: Epidemiology of osteoporotic fractures. *Osteoporos Int* 2005, 16 Suppl 2:S3–7. https://doi.org/10.1007/s00198-004-1702-6 PMID: 15365697
- Salpakoski A, Tormakangas T, Edgren J, Sihvonen S, Pekkonen M, Heinonen A, et al: Walking recovery after a hip fracture: a prospective follow-up study among community-dwelling over 60-year old men and women. *Biomed Res Int* 2014, 2014:289549. <u>https://doi.org/10.1155/2014/289549</u> PMID: 24511530
- Kohrt WM, Bloomfield SA, Little KD, Nelson ME, Yingling VR, American College of Sports M: American College of Sports Medicine Position Stand: physical activity and bone health. *Med Sci Sports Exerc* 2004, 36(11):1985–1996. https://doi.org/10.1249/01.mss.0000142662.21767.58 PMID: 15514517
- Warburton DE, Nicol CW, Bredin SS: Health benefits of physical activity: the evidence. CMAJ 2006, 174(6):801–809. https://doi.org/10.1503/cmaj.051351 PMID: 16534088
- Gregg EW, Pereira MA, Caspersen CJ: Physical activity, falls, and fractures among older adults: a review of the epidemiologic evidence. J Am Geriatr Soc 2000, 48(8):883–893. https://doi.org/10.1111/j. 1532-5415.2000.tb06884.x PMID: 10968291
- Sipila S, Tormakangas T, Sillanpaa E, Aukee P, Kujala UM, Kovanen V, et al: Muscle and bone mass in middle-aged women: role of menopausal status and physical activity. *J Cachexia Sarcopenia Muscle* 2020, 11(3):698–709. https://doi.org/10.1002/jcsm.12547 PMID: 32017473
- McVey MK, Geraghty AA, O'Brien EC, McKenna MJ, Kilbane MT, Crowley RK, et al: The impact of diet, body composition, and physical activity on child bone mineral density at five years of age-findings from the ROLO Kids Study. *Eur J Pediatr* 2020, 179(1):121–131. <u>https://doi.org/10.1007/s00431-019-03465-x PMID: 31673780</u>
- Kitamura K, Nakamura K, Kobayashi R, Oshiki R, Saito T, Oyama M, et al: Physical activity and 5-year changes in physical performance tests and bone mineral density in postmenopausal women: the Yokogoshi Study. *Maturitas* 2011, 70(1):80–84. https://doi.org/10.1016/j.maturitas.2011.06.014 PMID: 21782364
- Hauger AV, Holvik K, Bergland A, Stahle A, Emaus N, Morseth B, et al: Physical capability, physical activity, and their association with femoral bone mineral density in adults aged 40 years and older: The Tromso study 2015–2016. Osteoporos Int 2021. https://doi.org/10.1007/s00198-021-05949-9 PMID: 33864108
- Johansson J, Nordstrom A, Nordstrom P: Objectively measured physical activity is associated with parameters of bone in 70-year-old men and women. *Bone* 2015, 81:72–79. https://doi.org/10.1016/j. bone.2015.07.001 PMID: 26151120
- Daly RM, Ahlborg HG, Ringsberg K, Gardsell P, Sernbo I, Karlsson MK: Association between changes in habitual physical activity and changes in bone density, muscle strength, and functional performance in elderly men and women. J Am Geriatr Soc 2008, 56(12):2252–2260. https://doi.org/10.1111/j.1532-5415.2008.02039.x PMID: 19016934

- Augestad LB, Schei B, Forsmo S, Langhammer A, Flanders WD: Healthy postmenopausal womenphysical activity and forearm bone mineral density: the Nord-Trondelag health survey. *J Women Aging* 2006, 18(1):21–40. https://doi.org/10.1300/J074v18n01\_03 PMID: 16635948
- Morseth B, Emaus N, Wilsgaard T, Jacobsen BK, Jorgensen L: Leisure time physical activity in adulthood is positively associated with bone mineral density 22 years later. The Tromso study. *Eur J Epidemiol* 2010, 25(5):325–331. https://doi.org/10.1007/s10654-010-9450-8 PMID: 20349268
- Jacobsen BK, Eggen AE, Mathiesen EB, Wilsgaard T, Njolstad I: Cohort profile: the Tromso Study. Int J Epidemiol 2012, 41(4):961–967. https://doi.org/10.1093/ije/dyr049 PMID: 21422063
- Grimby G, Borjesson M, Jonsdottir IH, Schnohr P, Thelle DS, Saltin B: The "Saltin-Grimby Physical Activity Level Scale" and its application to health research. *Scand J Med Sci Sports* 2015, 25 Suppl 4:119–125. https://doi.org/10.1111/sms.12611 PMID: 26589125
- Omsland TK, Emaus N, Gjesdal CG, Falch JA, Tell GS, Forsen L, et al: In vivo and in vitro comparison of densitometers in the NOREPOS study. *J Clin Densitom* 2008, 11(2):276–282. <u>https://doi.org/10.1016/j.jocd.2007.10.001</u> PMID: 18158262
- Rao AD, Reddy S, Rao DS: Is there a difference between right and left femoral bone density? J Clin Densitom 2000, 3(1):57–61. https://doi.org/10.1385/jcd:3:1:057 PMID: 10745302
- Singer JDW, J. B.: Applied longitudinal data analysis: modeling change and event occurrence. Oxford; Toronto: Oxford University Press; 2003.
- 23. Kim J: How to Choose the Level of Significance: A Pedagogical Note. In., 13.3.2016 edn; 2015: 16.
- Lorentzon M, Mellstrom D, Ohlsson C: Association of amount of physical activity with cortical bone size and trabecular volumetric BMD in young adult men: the GOOD study. *J Bone Miner Res* 2005, 20 (11):1936–1943. https://doi.org/10.1359/JBMR.050709 PMID: 16234966
- Torstveit MK, Sundgot-Borgen J: Low bone mineral density is two to three times more prevalent in nonathletic premenopausal women than in elite athletes: a comprehensive controlled study. *Br J Sports Med* 2005, 39(5):282–287; discussion 282–287. <u>https://doi.org/10.1136/bjsm.2004.012781</u> PMID: 15849292
- 26. Hind K, Hayes L, Basterfield L, Pearce MS, Birrell F: Objectively-measured sedentary time, habitual physical activity and bone strength in adults aged 62 years: the Newcastle Thousand Families Study. J Public Health (Oxf) 2020, 42(2):325–332. https://doi.org/10.1093/pubmed/fdz029 PMID: 31220295
- Bemben DA, Bemben MG: Dose-response effect of 40 weeks of resistance training on bone mineral density in older adults. Osteoporos Int 2011, 22(1):179–186. https://doi.org/10.1007/s00198-010-1182-9 PMID: 20195844
- Watson SL, Weeks BK, Weis LJ, Harding AT, Horan SA, Beck BR: High-Intensity Resistance and Impact Training Improves Bone Mineral Density and Physical Function in Postmenopausal Women With Osteopenia and Osteoporosis: The LIFTMOR Randomized Controlled Trial. *J Bone Miner Res* 2018, 33(2):211–220. https://doi.org/10.1002/jbmr.3284 PMID: 28975661
- Lambert C, Beck BR, Harding AT, Watson SL, Weeks BK: Regional changes in indices of bone strength of upper and lower limbs in response to high-intensity impact loading or high-intensity resistance training. *Bone* 2020, 132:115192. https://doi.org/10.1016/j.bone.2019.115192 PMID: 31846824
- Kemmler W, Engelke K, von Stengel S: Long-Term Exercise and Bone Mineral Density Changes in Postmenopausal Women—Are There Periods of Reduced Effectiveness? J Bone Miner Res 2016, 31 (1):215–222. https://doi.org/10.1002/jbmr.2608 PMID: 26234411
- Augestad LB, Schei B, Forsmo S, Langhammer A, Flanders WD: The association between physical activity and forearm bone mineral density in healthy premenopausal women. *J Womens Health* (*Larchmt*) 2004, 13(3):301–313. https://doi.org/10.1089/154099904323016464 PMID: 15130259
- Delvaux K, Lefevre J, Philippaerts R, Dequeker J, Thomis M, Vanreusel B, et al: Bone mass and lifetime physical activity in Flemish males: a 27-year follow-up study. *Med Sci Sports Exerc* 2001, 33 (11):1868–1875. https://doi.org/10.1097/00005768-200111000-00011 PMID: 11689737
- Rikkonen T, Salovaara K, Sirola J, Karkkainen M, Tuppurainen M, Jurvelin J, et al: Physical activity slows femoral bone loss but promotes wrist fractures in postmenopausal women: a 15-year follow-up of the OSTPRE study. *J Bone Miner Res* 2010, 25(11):2332–2340. https://doi.org/10.1002/jbmr.143 PMID: 20533310
- Ramchand SK, David NL, Lee H, Eastell R, Tsai JN, Leder BZ: Efficacy of Zoledronic Acid in Maintaining Areal and Volumetric Bone Density After Combined Denosumab and Teriparatide Administration: DATA-HD Study Extension. *J Bone Miner Res* 2021, 36(5):921–930. <u>https://doi.org/10.1002/jbmr.4259</u> PMID: 33507574
- 35. Emaus A, Degerstrom J, Wilsgaard T, Hansen BH, Dieli-Conwright CM, Furberg AS, et al: Does a variation in self-reported physical activity reflect variation in objectively measured physical activity, resting

heart rate, and physical fitness? Results from the Tromso study. *Scand J Public Healt* 2010, 38:105–118. https://doi.org/10.1177/1403494810378919 PMID: 21062845

- 36. Sagelv EH, Hopstock LA, Johansson J, Hansen BH, Brage S, Horsch A, et al: Criterion validity of two physical activity and one sedentary time questionnaire against accelerometry in a large cohort of adults and older adults. *BMJ Open Sport Exerc Med* 2020, 6(1):e000661. https://doi.org/10.1136/bmjsem-2019-000661 PMID: 32153981
- Wilsgaard T, Emaus N, Ahmed LA, Grimnes G, Joakimsen RM, Omsland TK, et al: Lifestyle impact on lifetime bone loss in women and men: the Tromso Study. *Am J Epidemiol* 2009, 169(7):877–886. https://doi.org/10.1093/aje/kwn407 PMID: 19174426
- Matthew CE: Calibration of accelerometer output for adults. *Med Sci Sports Exerc* 2005, 37(11 Suppl): S512–522. https://doi.org/10.1249/01.mss.0000185659.11982.3d PMID: 16294114
- Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, et al: Predictive value of BMD for hip and other fractures. J Bone Miner Res 2005, 20(7):1185–1194. <u>https://doi.org/10.1359/JBMR.050304</u> PMID: <u>15940371</u>