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Does Bone Mineral Density Improve the Predictive Accuracy of Fracture Risk Assessment? A Prospective Cohort Study in Northern Denmark.

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Title

Does Bone Mineral Density Improve the Predictive Accuracy of Fracture Risk Assessment? A Prospective Cohort Study in Northern Denmark.

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We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

All authors have completed the ICMJE uniform disclosure form at <u>www.icmje.org/coi_disclosure.pdf</u> and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration

The lead author (Dr Dhiman) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical Approval

Ethics approval was given through the Region of North Jutland's from the Danish Data Protection Agency ("paraplyanmeldelse 2008-58-0028").

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Disclaimer

The views expressed are those of the author(s) and not necessarily those of the NIHR, the NHS or the Department of Health.

Patient Involvement

Patients were not involved in the development of this research question.

Data Sharing Statement

Data sharing: Technical appendix and statistical code is available from the corresponding author at paula.dhiman@nottingham.ac.uk. Due to restrictions by the Danish Data Protection Agency, data can only be shared on an aggregated level and by special permission.

Contributorship

Contributors: PD wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. PV and SA provided the AURORA dataset for analysis and linked patients to the National Patient Registry of Denmark, they also reviewed and revised the draft paper. NQ and TM provided clinical expertise, and reviewed and revised the draft paper.

Abstract:

Objective: To evaluate the added predictive accuracy of bone mineral density (BMD) to fracture risk assessment.

Design: Prospective cohort study using data between 01/01/2010 and 31/12/2012.

Setting: North Denmark Osteoporosis Clinic of referred patients presenting with at least one fracture risk factor to the referring doctor.

Participants: Patients aged 40-90 years; had BMD T-score recorded at the hip; and not taking osteoporotic preventing drugs for more than 1-year prior to baseline.

Main outcome measures: Incident diagnoses of osteoporotic fractures (hip, spine, forearm, humerus, or pelvis) were identified using the National Patient Registry of Denmark during 01/01/2012-01/01/2014. Cox regression was used to model predictors based on Fracture Risk Assessment Tool (FRAX®), with and without, binary and continuous BMD. Change in Harrell's C-Index and Reclassification tables were used to describe the added statistical value of BMD.

Results: Adjusting for predictors included in FRAX®, osteoporotic patients (T-score \leq -2.5) had 75% higher hazard of a fracture compared to patients with higher BMD (HR:1.75 (95% CI:1.28 to 2.38)). Forty-percent lower hazard was found per unit increase in continuous BMD T-score (HR:0.60 (95% CI:0.52 to 0.69)).

Accuracy improved, and Harrell's C-Index increased by 1.2% when adding continuous BMD (0.76 to 0.77). Reclassification tables showed continuous BMD shifted 463 patients into different risk categories; 274 of these were reclassified correctly (59%; 95% CI:55% to 64%). Adding binary BMD however showed little impact: Harrell's C-Index decreased by 0.6% and correctly reclassified 71 out of 109 patients (65%; 95% CI:55% to 74%).

Conclusions: Bone mineral density improves fracture risk prediction and should be incorporated in routine fracture risk assessment. Performance measures showed that using BMD in a continuous format is better than using a binary format. The added value of BMD to fracture risk prediction should be confirmed using routinely collected primary care data in other countries.

Article Summary

Strengths and Limitations:

- Addresses a research question recommended by The National Institute for Health and Care Excellence to investigate the added value of bone mineral density to fracture risk prediction.
- Investigates bone mineral density in both the commonly used, binary, and continuous format.
- Uses robustly collected data from Northern Denmark, with 3.2% missing data.
- As data is from a North Danish population, with at least one fracture risk factor, this limits generalisability of the results.
- Explores replacing current fracture risk factors, as well as adding to them, with bone mineral density.

Introduction

Osteoporosis causes over 8.9 million fractures worldwide, of which over 4.5 million occur in the USA and Europe, and account for 2.8 million disability adjusted life years (1). Further, 1.2 million disability adjusted life years are accounted for by hip fractures, which are projected to increase to 6 million by 2050 (2).

Given this burden, and treatment options for osteoporosis, identifying patients at risk of an osteoporotic fracture is high priority amongst health policymakers to reduce the risk of future fracture (3). Risk prediction tools have been developed to aid in the identification of patients at risk. For example, the Fracture Risk Assessment Tool (FRAX®) and QFracture® are commonly used to assess fracture risk in patients based on pre-defined risk factors.

Bone mineral density (BMD), a measurement used to aid diagnosis of osteoporosis, has also been identified as a fracture risk factor (4-7). Unlike some other fracture risk factors, treatment options (e.g. bisphosphonate medication) are available that reduces the fracture risk markedly when treatment is initiated based on low BMD.

English National guidelines (The National Institute for Health and Care Excellence (NICE)) for fracture risk assessment recommend treatment of osteoporosis to prevent fractures but have not included BMD as a mandatory risk factor for fracture risk prediction tools to incorporate (8). This is partly due to the lack of robust evidence and limited generalisability of current research, which has particularly focused on evaluating BMD in postmenopausal women evaluating the added value of BMD to existing fracture risk factors (5-7).

The National Institute of Clinical Health and Excellence also recognise this gap in the evidence and have recommended research to assess the added value of BMD as a risk factor in fracture risk assessment (9).

The aim of this study is to assess the value of BMD measurement in addition to the standard fracture risk factors used in the FRAX® risk model using a robustly collected prospective cohort.

Methods

This paper has been written in accordance to the TRIPOD checklist.

Patient Involvement

Patients were not involved in the development of this research question and were not involved in the design of this study.

Study Design and Data Source

A prospective cohort study was conducted using patients from the Aalborg University Hospital Record for Osteoporosis Risk Assessment (AURORA) dataset; patients were followed up using the National Patient Registry of Denmark.

The AURORA dataset consists of patients attending the Osteoporosis Clinic at Aalborg University Hospital after a referral from their primary care physician. A referral was offered to patients with at least one risk factor for osteoporosis (low BMI, previous fracture, parental hip fracture, smoking status, alcohol consumption, glucocorticoid use, rheumatoid arthritis, and secondary osteoporosis) or if they were aged 80 years and above. Further detail of the data collection has been described elsewhere (10). The Danish National Patient Registry which collects inpatient and outpatient data from all Danish hospitals, was linked to the AURORA dataset through unique patient identifiers

Ethics approval was given through the Region of North Jutland's from the Danish Data Protection Agency ("paraplyanmeldelse 2008-58-0028").

Cohort selection

Data collection for AURORA began 1st January 2010 and was collected for 3 years (up to 31st December 2012). Patients were included if they were aged 40-90 years; had a BMD T-score at the hip; and were not taking any osteoporotic preventing drugs or any bone sparing drugs for more than one year prior to baseline.

Primary Outcome

The primary outcome measure was an incident osteoporotic fracture during follow up (01/01/2012 to 01/01/2014); defined as a diagnosis of a fracture at the hip, spine, forearm, humerus, and pelvis. Fractures at these sites resulting from traffic, work, and sports related accidents were excluded from the study. Relevant fractures were identified in the Danish National Patient Registry, using the International Statistical Classification of Diseases, 10th Version codes (ICD-10 codes), which was developed using recognised database methodology for each fracture (11).

Fracture risk factors

Fracture risk factors, used in the FRAX® risk prediction model, were extracted at baseline. They were: age; gender; height (m); weight (kg); previous fracture; parental history of hip fracture, current smoking status; current alcohol consumption; glucocorticoid use (currently exposed for 3+ months); rheumatoid arthritis; and secondary osteoporosis (includes type I diabetes; osteogenesis imperfecta in adults; untreated, long standing hyperthyroidism;

hypogonadism; premature menopause (<45 years); chronic malnutrition; malabsorption; and chronic liver disease).

Bone Mineral Density

DXA scans were performed by trained technicians using Hologic Discovery A (Bedford, MA, USA). A daily QC programme was in place and in vivo CV using repositioning of patients was <1%. Total hip BMD was used as region of interest. Bone mineral density was added to the fracture risk prediction model twice, firstly, as a continuously measured T-score value, and secondly, as a binary risk factor, dichotomised at/above T-score threshold for osteoporosis and below threshold, -2.5 in T-score (manufacturers' normal range using normal material from T Kelly et al (12)) based on World Health Organisation (WHO) classifications (13).

Statistical Analysis

A complete case analysis was performed on the data, 3.2% of data was missing. The AURORA dataset was split into two using recognised methodology (14); where a randomly was assigned to patients and based on a cut off two-thirds was used to derive the risk models, and the remaining third was used to validate them.

Model derivation

Five Cox proportional hazards models were developed for the primary outcome, using a complete case analysis:

- Model 1. Standard fracture risk factors only (without BMD)
- Model 2. Standard fracture risk factors (with binary BMD)
- Model 3. Standard fracture risk factors (with continuous BMD)
- Model 4. Data driven standard fracture risk factors (with binary BMD)
- Model 5. Data driven standard fracture risk factors (with continuous BMD)

Graphical methods were used (log-log plots) to assess the proportional hazards assumption, and risk factors violating this assumption were added to the model as a time varying covariate. Data driven models were developed by removing risk factors which were not statistically significant, based on p-value<0.05, when adding continuous or binary BMD measurement.

Recognised methodology used in research studies was used to build the 5 risk prediction models (15, 16); the Kaplan Meier method was used to obtain 4-year fracture risk estimates for patients. Further detail on the conversion of the Cox proportional hazards models to risk prediction models has been provided in Supplementary Table 1.

Validation of Models

Four-year fracture risk was calculated from each model and the predictive performance of each risk prediction model was assessed by measures describing calibration, discrimination, and reclassification.

Calibration measures how well the predicted risk agrees with observed risk in the data. It plots the mean predicted and observed risk of fracture for each decile of predicted risk. The

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observed risk of fracture was derived from the 4 year Kaplan-Meier estimate. Good calibration indicates the predicted risk is close to the observed risk of the outcome.

Discrimination measures how well the risk prediction model differentiates between patients who have or have not observed the event in the study. This was quantified by the area under the receiver operating characteristic (ROC) curve (AUC), given by Harrell's C-Index with higher values indicating better discrimination.

Reclassification tables (17) measures movement between risk categories when adding a new risk factor. Threshold for treatment at 4 years was set at a fracture risk level of 8.5%; to be comparable to the treatment threshold of 20% at 10 years. This was presented by the total percent of patients reclassified (incorrectly and correctly), and also the Net Reclassification Index (NRI) (18, 19). The NRI gives the net calculation of the changes in the right direction and a higher NRI indicates a better reclassifying model.

All analyses were carried out using Stata (version 12) (20).

Results

Characteristics of the data

The AURORA collected data on 7,912 patients; 1,795 patients were excluded comprising, 440 not aged between 40-90 years at baseline; 156 not having a recorded T-score value for the total hip at baseline; and 1,199 patients were taking anti-osteoporotic drug therapy for more than one year prior to baseline.

The study sample consisted of 6,117 patients; predominantly female (79.6%), and patients with a mean age of 62.9 (SD: 10.9) years. Two-thirds of this sample (n=4,093) was used for the derivation dataset and one-third (n=2,094) was used for the validation dataset. Table 1 presents the baseline characteristics of the study by derivation and validation dataset, and shows little difference between the datasets.

Patients in the derivation dataset observed 318 (7.8%) osteoporotic fractures during follow up. Of these, 316 fractures were eligible for the analysis (2 patients had a fractures on or prior to baseline and were excluded). Patients contributed 9352.8 person years of observation, giving a total incidence rate of 337.87 per 10,000 person years (95% CI:302.60 to 377.25).

Fractures during follow up were predominantly found in the forearm (27.0%) and hip (17.9%). Higher fracture incidence rates were found in patients classed as osteoporotic, based on their T-score at both the femoral neck (809.73 per 10,000 person years (95% CI:641.68 to 1021.78)) and spine (L1-L4) (553.59 per 10,000 person years (95% CI:462.55 to 662.55)) (Supplementary Table 2).

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Table 1. Baseline characteristics of the derivation	and validation	datasets, including	missing
data.			

Characteristic			Deriv (n=4	ation ,093)	Valid (n=2	ation ,024)
			No	%	No	%
Gender	Female		3,266	79.79	1,602	79.15
	Male		827	20.21	422	20.85
Osteoporotic (Hip DXA)	No		3,683	89.98	1,820	89.92
	Yes		410	10.02	204	10.08
Osteoporotic Status (based on	Normal		1,886	46.08	927	45.8
UK guidelines)	Osteopenic		1,797	43.90	893	44.12
	Osteoporotic		410	10.02	204	10.08
Previous Fracture	No		2,935	71.71	1,423	70.31
	Yes		1,158	28.29	601	29.69
No of Previous Fractures	None		2,935	71.71	1,423	70.31
	1 fracture		862	21.06	467	23.07
	2-4 fractures		270	6.60	122	6.03
	5+ fractures		26	0.64	12	0.59
Parental History of Hip Fracture	No		2,755	67.31	1,359	67.14
	Yes		1,338	32.69	665	32.86
Current Smoking Status	other (non/ex)		3,182	77.74	1,529	75.54
	smoker		911	22.26	495	24.46
Alcohol Consumption	<3		3,875	94.67	1,923	95.01
	>3 units		218	5.33	101	4.99
Glucocorticoid Use	No		3,577	87.39	1,741	86.02
	Yes		516	12.61	283	13.98
Rheumatoid Arthritis	No		3,686	90.06	1,801	88.98
	Yes		407	9.94	223	11.02
Other Bone Affecting Disease	No		2,382	58.20	1,139	56.27
	Yes	\mathbf{O}	1,711	41.80	885	43.73
Secondary Osteoporosis	No		3,438	84.00	1,689	83.45
	Yes		655	16.00	335	16.55
	By disease					
	Type 1 diabetes	No	4,010	97.97	1,981	97.88
		Yes	83	2.03	43	2.12
	Osteogenesis	No	4,093	100	2,024	100
		Yes	0	0	0	0
	Hypothyroidism	No	4,089	99.9	2,023	99.95
		Yes	4	0.1	1	0.05
	Malnutrition	No	4,090	99.93	2,023	99.95
		Yes	3	0.07	1	0.05
	Chronic Liver Disease	No	4,006	97.87	1,979	97.78
		Yes	87	2.13	45	2.22
	Menopause (Females only)**	No	853	20.84	405	20.01
		Yes	2,413	58.95	1,197	59.14

	Premature Menopause (<45years)***	No	1,904	46.52	941	46.49
		Yes	509	12.44	256	12.65
			Mean	SD	Mean	SD
Age (years)			62.91	10.92	62.99	10.96
Weight (kg)			72.12	15.47	72.23	15.86
	Missing		47	1.15	12	0.59
Height (m)			1.65	0.08	1.65	0.08
	Missing		131	3.2	61	3.01
BMI			26.39	5.04	26.39	5.13
	Missing		135	3.3	63	3.11
Hin DXA T-score			_1 13	1.00	-1.16	1.08

*out of patients with a fracture

**proportion out of respective number of females

***proportion out of respective number of females with menopause

Model development

The unadjusted analysis showed statistically significant association between BMD (continuous and binary) and osteoporotic fracture (p<0.001). Significant associations with fracture were also found with age (p<0.001), previous fracture (p<0.001), BMI (p=0.03), and gender (p=0.05). Further, a time-varying effect was found in patients with a previous fracture; hazard of a subsequent fracture was highest in the first year during follow up and decreased per year of follow up (p<0.001).

The adjusted analysis is presented in Table 2. Model 1 showed that of the standard risk factors, age and previous fracture were significantly associated with fracture; hazard of fracture increased by 2% per year increase in age (HR=1.02; 95% CI: 1.01 to 1.04); and increased almost 5 fold in patients with a previous fracture (HR=4.88; 95% CI: 3.37 to 7.08).

Adding binary and continuous BMD to standard risk factors (Model 2) led to 75% increased hazard of fracture (HR=1.75; 95% CI: 1.28 to 2.38), whilst adding continuous BMD T-score (Model 3) led to a 40% lower hazard per SD improvement in BMD T-score (HR=0.60; 95% CI: 0.52 to 0.69).

Insignificant risk factors were also removed (Model 4 and 5). Removing secondary osteoporosis when adding binary BMD (Model 4), and removing secondary osteoporosis, current smoker, and BMI, when adding continuous BMD gave similar results but simplified the model.

Table 2. Multivariate analysis for osteoporotic fracture in the derivation cohort. Data are adjusted hazard ratios and 95% confidence intervals.

		Adjusted Hazard Ratio (95% CI)					
Risk Factor		Model 1: Standard Risk Factors only	Model 2: Standard Risk Factors + BMD (categorical)	Model 3: Standard Risk Factors + BMD (continuous)	Model 4: Data Driven Standard Risk Factors + BMD (categorical)	Model 5: Data Driven Standard Risk Factors + BMD (continuous)	
Age (years)		1.02 (1.01 to 1.04)	1.02 (1.01 to 1.03)	1.01 (1.00 to 1.02)	1.02 (1.01 to 1.03)	1.01 (1.00 to 1.02)	
Gender	Female	Ref	Ref	Ref	Ref	Ref	
Gender	Male	0.75 (0.54 to 1.04)	0.80 (0.57 to 1.10)	0.85 (0.61 to 1.18)	0.80 (0.58 to 1.11)	0.86 (0.62 to 1.20)	
BMI		0.98 (0.95 to 1.00)	0.99 (0.96 to 1.01)	1.03 (1.00 to 1.05)	0.99 (0.96 to 1.01)	-	
Dravious Fracture	No	Ref	Ref	Ref	Ref	Ref	
Previous Fracture	Yes	4.88 (3.37 to 7.08)	4.67 (3.21 to 6.78)	4.02 (2.76 to 5.84)	4.66 (3.21 to 6.77)	4.09 (2.82 to 5.95)	
Demonstral Higtory, of Him Encodyna	No	Ref	Ref	Ref	Ref	Ref	
Parental History of Hip Fracture	Yes	1.08 (0.83 to 1.40)	1.10 (0.85 to 1.42)	1.11 (0.85 to 1.43)	1.10 (0.85 to 1.42)	1.10 (0.85 to 1.42)	
Comment Surgloom	No	Ref	Ref	Ref	Ref	Ref	
Current Smoker	Yes	1.12 (0.85 to 1.47)	1.08 (0.82 to 1.42)	1.02 (0.77 to 1.34)	1.07 (0.82 to 1.41)	-	
Also $h = 1$ Composition (5.2 cm $\frac{1}{2}$	No	Ref	Ref	Ref	Ref	Ref	
Alconol Consumption (>3 units/day)	Yes	1.41 (0.90 to 2.21)	1.44 (0.92 to 2.25)	1.04 (0.72 to 1.49)	1.44 (0.92 to 2.25)	1.43 (0.92 to 2.22)	
Characterid	No	Ref	Ref	Ref	Ref	Ref	
Giucocorticola Use	Yes	1.08 (0.75 to 1.55)	1.05 (0.73 to 1.51)	1.46 (0.93 to 2.28)	1.05 (0.73 to 1.51)	1.04 (0.73 to 1.49)	
Dhoumataid Arthritic	No	Ref	Ref	Ref	Ref	Ref	
Rheumatoid Arthitus	Yes	1.10 (0.73 to 1.65)	1.09 (0.72 to 1.64)	1.12 (0.74 to 1.68)	1.09 (0.73 to 1.64)	1.12 (0.75 to 1.69)	
Sacan dam. Ostacan anacis	No	Ref	Ref	Ref	Ref	Ref	
Secondary Osteoporosis	Yes	0.99 (0.73 to 1.35)	0.97 (0.71 to 1.32)	0.91 (0.67 to 1.24)	-	-	
Osteoporotic	No	Ref	Ref	Ref	Ref	Ref	
	Yes	-	1.75 (1.28 to 2.38)	-	1.74 (1.28 to 2.38)	-	
Hip DXA T-score (SD)		-	-	0.60 (0.52 to 0.69)	-	0.64 (0.57 to 0.72)	
Previous Fracture (TVC [*])		0.64 (0.49 to 0.83)	0.64 (0.49 to 0.83)	0.64 (0.50 to 0.84)	0.64 (0.49 to 0.83)	0.64 (0.50 to 0.84)	

*TVC = time varying covariate

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Model Validation

The 4-year predicted risk of fracture was calculated for all patients in the validation dataset; this was compared to the observed fracture outcome within the 4 year follow up.

Calibration and Discrimination

Calibration improved when adding BMD measurement; particularly when including continuous BMD T-score measurement (Model 3; Supplementary Figure 1).

The largest change in discrimination was found when adding continuous BMD measurement to standard risk factors; Harrell's C-Index increased by 1.15% (Table 3). However, binary BMD measurement, as a measure for osteoporotic patients, was found to reduce Harrell's C-Index by -0.62%.

Table 3. Harrell's C-Index for Model 1, 2, 3, 4, and 5.

Model	Harrell's C-Index	Change in Harrell's C-Index (% change)*
Model 1: Standard fracture risk factors only (without BMD)	0.7640 (0.7181 to 0.8099)	-
Model 2 : Standard fracture risk factors only (with binary BMD)	0.7592 (0.7124 to 0.8061)	-0.0048 (-0.62%)
Model 3 : Standard fracture risk factors only (with continuous BMD)	0.7728 (0.7317 to 0.8139)	0.0088 (1.15%)
Model 4: Data driven standard fracture risk factors (with binary BMD)	0.7587 (0.7118 to 0.8056)	-0.0053 (-0.69%)
Model 5 :Data driven standard fracture risk factors (with continuous BMD)	0.7707 (0.7294 to 0.8120)	0.0067 (0.88%)

*All change is measures against Model 1.

Reclassification

Reclassification tables showed risk models with continuous BMD measurement improved classification of patients into their correct risk categories. This was not found when adding binary BMD. Table 4 presents the reclassification table for Model 1 (standard fracture risk factors only) and Model 3 (standard risk factors with continuous BMD), using the 8.5% prespecified risk threshold.

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			Model 3: continuo	SRF with us BMD		
			<8.5%	≥8.5%	Total	Total No.(%) Reclassified
		No	391	227		
		%	63.27%	36.73%		
Model 1: SRF	<8.5%	No. Events	5	9	618	227 (36.73%)
without BMD		No. Non events	386	218		
DIVID	C	Observed Event Rate	1.28%	3.96%		
	•	No	302	1,040		
		%	22.50%	77.50%		
	≥8.5%	No. Events	10	121	1,342	302 (22.5%)
		No. Non events	292	919		
		Observed Event Rate	3.31%	11.63%		
	Total		693	1,267	1,960	529 (26.99%)

Table 4. Risk Reclassification Table comparing Model 1 (standard fracture risk factors alone) to Model 3 (standard fracture risk factors with continuous BMD measurement), using a clinical 8.5% risk cut off.

Of the 1,960 patients in the validation dataset, 27% (n=529) were reclassified into a different risk category when including continuous BMD into fracture risk prediction. Two percent (9/529) were found to be reclassified correctly into a higher risk group and 55% (292/529) were reclassified correctly into a lower risk group; indicating 22% (292/1342) of patients at high risk in Model 1, not accounting for BMD measurement, were no longer at high risk. The net reclassification improvement when adding continuous BMD to standard risk factors, was 0.03, similar results were found when comparing Model 1 with the data driven models (Table 5).

Table 5. Summary of Net Reclassification Index (NRI) and Integrated Discrimination Index (IDI) for all comparisons between developed fracture risk prediction models.

Comparison	Event NRI	Non-Event NRI	Overall NRI
Model 1 vs. Model 2	-3.45%	2.09%	-0.01
Model 1 vs. Model 3	-0.69%	4.08%	0.03
Model 1 vs. Model 4	-4.14%	1.98%	-0.02
Model 1 vs. Model 5	-0.69%	4.74%	0.04

Discussion

Summary of Findings

Bone mineral density improved fracture risk prediction. This finding was consistent throughout the analysis; both the unadjusted and adjusted analyses. However, the format of BMD measurement in the fracture risk prediction model affected the results. Calibration, discrimination, and reclassification all improved when adding continuous BMD measurement to standard risk factors. This was not found when adding BMD in a binary format.

Adding BMD to fracture risk prediction model negated the effect of fracture with secondary osteoporosis, current smoking status, and BMI. Removing these risk factors had minimal impact on the model performance.

Strengths and Limitations

Answering Evidence gap

To our knowledge, this is the first study to investigate the added value of BMD in a binary and continuous format, to standard fracture risk factors. It directly informs the NICE research recommendation to assess the added value of BMD to routine fracture risk assessment in primary care (21). It further highlights that the more commonly used, binary format of BMD resulted in a loss of predictability in fracture risk prediction; based on comparable measures for discrimination and reclassification

Robustness of Data

The prospective cohort was well populated with key standard risk factors recorded: BMI, smoking status and alcohol consumption, and personal and parental fracture history. Other than 3.2% of missing data for BMI, in 6,117 patients, complete data was collected for all risk factors (including BMD T-score recorded at the total hip). Further, the cohort was linked to a national robust electronic health records. This Danish National Patient Registry allowed for outcome fracture to be identified and also provided data on the mechanism for the fracture; this helped more accurately phenotype osteoporotic fractures.

Generalisability

The generalisability is affected in two ways. Firstly, the findings are based on a Danish cohort. Secondly, AURORA data was collected from patients who presented to their doctor with at least one fracture risk factor and were referred to the osteoporosis clinic; this led to a biased study sample with a higher risk of a fracture and increased age. This could overestimate fracture risk amongst patients in a primary care setting.

Methodology

As well as assessing the added value of BMD to standard, we have also explored the option to replace existing fracture risk factors with the BMD measurement; this has rarely been explored in the literature but should be considered in future analyses. (22, 23).

Due to the increased age of the sample, death becomes a competing risk. However, information on death was not collected and could not be retrieved. This limited the analysis of the data as competing risks could not be accounted for which may again lead to an

overestimation of fracture risk (24). However, as an independent study primarily assessing the added value of BMD through deriving and validating the fracture risk prediction models, this bias would be present in both analyses to compare derived risk models with and without BMD measurement.

Internal validation was performed to validate the derived risk prediction models. This may lead to over optimistic results of the performance of the risk models (14). To account for this limitation, a commonly practised method which randomly assigns patients to the derivation and validation datasets was used; further, a similar 1:3 ratio was also used to split the data (25-27).

The study had a 4 year follow up which is shorter than other recognised risk models. To account for this, we adapted the 20% clinical risk threshold for 10 year fracture estimates to 8.5% for 4 year fracture estimates (28, 29).

Traditional methodology assessing the added value to risk factors to existing risk prediction models are criticised to be insensitive to change, to lack interpretability (30-33); and do not account for cost implications. Reclassification analysis was used to provide more clinically interpretable results.

Clinical implications

The most notable clinical implication is the more routine use of BMD measurement for fracture risk assessment. Further, evidence suggests continuous BMD adds better predictability compared to the binary format.

Future Research

Further research is recommended to evaluate the added value of BMD to fracture risk prediction; in particular using primary care routinely collected data. However, a brief interrogation into the Clinical Practice Research Datalink, a routinely collected UK primary care database, showed poor availability of BMD measurement in patient records, and thus, strong limitations to potential analyses. Less than 1% of patients had BMD recorded from a sample of 60,658 patients aged 40-90; not on any osteoporotic treatment; and with complete data for age, gender, BMI, smoking status, and alcohol consumption. Thus, prior to UK analysis, BMD recording in primary care databases needs to improve.

In addition, further research is recommended to develop current methodology used to assess the added value of BMD to provide more clinically relevant results, such as cost implications; and to allow for better comparability between new risk factors with respect to their added value, thus improving decision making.

Conclusion

BMD improves fracture risk assessment, and may replace some standard fracture risk factors. However, improved performance of the fracture risk assessment was only demonstrated when using continuous BMD measurement for osteoporosis. Research is recommended to explore replacing existing risk factors as well as adding new risk factors to established models; develop more clinically relevant methodology to assess the added value of a new risk factor.

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Supplementary Information

Beta coefficients from each Cox regression model were used to create each fracture risk prediction model.

Once all 5 models were finalised, their beta coefficients were used to create 5 risk prediction models and calculate risk of fracture for each patient, using the following general equation:

$$\widehat{risk} = 1 - S_0(t)^{exp(\sum_{i=1}^p \beta_i X_i - \sum_{i=1}^p \beta_i \overline{X}_i)}$$

Where $S_0(t)$ is the baseline survival rate at follow up time, t(for this example, a follow up time of 10 years will be used); beta (β_i) are the regression coefficients for each included risk factor in the model (i); X_i is the observed data value for each risk factor; \overline{X}_i is the corresponding mean for each risk factor; and \mathbf{p} is the total number of risk factors included in the model. Table A1 shows the formula for each risk prediction model explicitly.

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0.3465287*mean alcohol consumption+0.0936966*mean rheumatoid arthritis+ -0.0069432*mean secondary osteoporosis+-0.4535108*mean (previous fracture) where $\sum_{l=1}^{p} \beta_l X_l =$ 0.0186827*age+-0.228784*gender+-0.0113651*BMI+1.540559*previous fractu 0.092011*parental hip fracture+0.0732564*smoking status+0.0508706*glucoco 0.3649544*alcohol consumption+0.0854353*rheumatoid arthritis+ -0.0346885* osteoporosis+0.5568944*osteoporosis+-0.4481145*(previous fracture*time) where $\sum_{l=1}^{p} \beta_l \overline{X}_l =$ 0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+ 1.540559*mean previous fracture+0.092011*mean parental hip fracture+ 0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+ 0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis+ -0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+ -0.4481145*mean (previous fracture*time)		0.1138883*mean smoking status+0.0773898*mean glucocorticoid use+
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1.540559*mean previous fracture+0.092011*mean parental hip fracture+ 0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+ 0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis+ -0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+ -0.4481145*mean (previous fracture*time)		0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+
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0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis+ -0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+ -0.4481145*mean (previous fracture*time) <i>[Table continues on the next page]</i>		0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+
-0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+ -0.4481145*mean (previous fracture*time) <i>[Table continues on the next page]</i>		0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis+
-0.4481145*mean (previous fracture*time) [Table continues on the next page]		-0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+
[Table continues on the next page]		-0.4481145*mean (previous fracture*time)
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Supplementary Table 1. Risk equations to calculate 4 year risk based on patient characteristics for each

Risk Model cont.	Equation
	where $\sum_{i=1}^{p} \beta_i X_i =$
	0.0071931*age+-0.1615582*gender+0.0268478*BMI+1.39069*previous fracture+
	0.1000272*parental hip fracture+0.0192416*smoking status+0.0374944*glucocorticoid us
	0 3774416*alcohol consumption+0 1097646*rheumatoid arthritis+ -0 0932063*secondary
	osteonorosis+-0 5110986*t-score+-0 4404955*(previous fracture*time)
	where $\nabla^p = \beta_1 \overline{X}_2$ =
Model 3	where $\mathcal{L}_{i=1}^{i} \mathcal{P}_{i} \mathcal{R}_{i}$ =
	0.00/1931+mean age+-0.1615382+mean gender+0.0268478+mean BMI+
	1.39069*mean previous fracture+0.1000272*mean parental hip fracture+
	0.0192416*mean smoking status+0.0374944*mean glucocorticoid use+
	0.3774416*mean alcohol consumption+0.1097646*mean rheumatoid arthritis+
	-0.0932063*mean secondary osteoporosis+-0.5110986*mean t-score+
	-0.4404955*mean (previous fracture*time)
	where $\sum_{i=1}^{p} \beta_i X_i =$
NA 114	0.0187859*age+-0.2242276*gender+-0.0114226*BMI+1.539469*previous fracture+
Model 4	0.0930207*parental hip fracture+0.0697597*smoking status+0.0509313*glucocorticoid us
	0.3635054*alcohol consumption+0.0859078*rheumatoid arthritis+0.5549807*osteoporosi
	-0.4478827*(previous fracture*time)
	where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$
	0.0187859*mean age+-0.2242276*mean gender+-0.0114226*mean BMI+
	1.539469*mean previous fracture+0.0930207*mean parental hip fracture+
	0.0697597*mean smoking status+0.0509313*mean glucocorticoid use+
	0.3635054*mean alcohol consumption+0.0859078*mean rhoumatoid arthritis+
	0.5540807* mean actor consumption + 0.0839078 mean incumation attinuity
	0.554980/*mean osteoporosis+-0.44/882/*mean (previous fracture*time)
	[Table continues on the next page]
Risk Model	Equation

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fracture+ 0.0412411*glucocorticoid use+0.3579932*alcohol consumption+

0.0095458*age+-0.1452714*gender+1.409116*previous fracture+0.0923278*parental hip

0.1144666*rheumatoid arthritis+ -0.4434596*t-score+-0.4403983*(previous fracture*time)

0.0095458*mean age+-0.1452714*mean gender+1.409116*mean previous fracture+

.u

0.0923278*mean parental hip fracture+0.0412411*mean glucocorticoid use+

0.3579932*mean alcohol consumption+0.1144666*mean rheumatoid arthritis+

-0.4434596*mean t-score+-0.4403983*mean (previous fracture*time)

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cont.

Model 5

where $\sum_{i=1}^{p} \beta_i X_i =$

where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$

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Supplementary Table 2. Crude fracture incidence rates for the derivation and validation data	isets.
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Risk Factor		Derivation			Validation			
		No of incident cases	Total Person years	Crude Incidence Rate per 10000 person years (95% CI)	No of incident cases	Total Person years	Crude Incidence Rate per 10000 person years (95% CI)	
	40-49	17	1169.9	145.31 (90.33 to 233.74)	12	557.8	215.15 (122.19 to 378.84)	
	50-59	70	2534.7	276.17 (218.49 to 349.07)	33	1311.0	251.71 (178.95 to 354.06)	
A ao Cotogory	60-69	93	3062.9	303.63 (247.79 to 372.06)	42	1453.9	288.87 (213.48 to 390.88)	
Age Categoly	70-79	83	1906.0	435.46 (351.17 to 539.98)	49	958.7	511.11 (386.29 to 676.26)	
	80-89	52	652.7	796.75 (607.13 to 1045.59)	16	347.4	460.56 (282.15 to 751.77)	
	90-99	1	26.6	376.51 (53.04 to 2672.85)	-	-	-	
Osteoporotic - Hip	No	245	8475.9	289.05 (255.03 to 327.61)	123	4165.1	295.31 (247.48 to 352.40)	
	Yes	71	876.8	809.73 (641.68 to 1021.78)	29	463.8	625.28 (434.52 to 899.78)	
Osteoporotic - Spine	No	191	7025.8	271.86 (235.91 to 313.28)	111	3475.6	319.37 (265.16 to 384.67)	
	Yes	119	2149.6	553.59 (462.55 to 662.55)	39	1089.1	358.08 (261.63 to 490.10)	
Gender	Female	266	7417.5	358.61 (318.01 to 404.40)	129	3679.8	350.56 (295.00 to 416.59)	
	Male	50	1935.3	258.36 (195.82 to 340.88)	23	949.0	242.36 (161.05 to 364.71)	
Parental History Hip	No	220	6281.5	350.24 (306.88 to 399.71)	118	3108.7	379.58 (316.92 to 454.64)	
Fracture	Yes	96	3071.3	312.57 (255.90 to 381.79)	34	1520.2	223.66 (159.81 to 313.02)	

[Table continues on the next page]

			D	Derivation	Validation			
Risk Factor cont.		No of incident cases	Total Person years	Crude Incidence Rate per 10000 person years (95% CI)	No of incident cases	Total Person years	Crude Incidence Rate per 10000 person years (95% CI)	
Current Smoker	No	240	7279.1	329.71 (290.53 to 374.18)	103	3513.1	293.19 (241.70 to 355.65)	
Current Shloker	Yes	76	2073.7	366.5 (292.71 to 458.90)	49	1115.8	439.16 (331.91 to 581.07)	
Alcohol Consumption	No	293	8875.9	330.11 (294.39 to 370.15)	140	4399.7	318.2 (269.63 to 375.53)	
more than 3 units per day	Yes	23	476.9	482.33 (320.52 to 725.83)	12	229.2	523.66 (297.39 to 922.09)	
Glucocorticoid Use (3	No	279	8184.5	340.89 (303.15 to 383.33)	132	3993.1	330.57 (278.73 to 392.06)	
months)	Yes	37	1168.3	316.7 (229.47 to 437.11)	20	635.8	314.57 (202.95 to 487.59)	
Manonausa	No	68	1962.8	346.44 (273.15 to 439.39)	29	928.9	312.19 (216.94 to 449.24)	
Wenopause	Yes	198	5454.7	362.99 (315.79 to 417.24)	100	2750.9	363.52 (298.82 to 442.23)	
Premature Menopause	No	280	8175.4	342.49 (304.64 to 385.05)	127	4032.1	314.97 (264.69 to 374.81)	
(<45 years)	Yes	36	1177.4	305.76 (220.56 to 423.89)	25	596.8	418.92 (283.07 to 619.97)	
BMI - low (<18.5)	No	289	8876.1	325.59 (290.14 to 365.38)	141	4367.0	322.87 (273.75 to 380.82)	
	Yes	11	187.0	588.16 (325.72 to 1062.04)	4	124.0	322.63 (121.09 to 859.62)	
Rheumatoid Arthritis	No	289	8457.8	341.70 (304.49 to 383.45)	139	4135.1	336.15 (284.66 to 396.94)	
And	Yes	27	895.0	301.69 (206.90 to 439.93)	13	493.8	263.29 (152.88 to 453.43)	

[Table continues on the next page]

		Derivation			Validation			
Risk Factor cont.		No of incident cases	Total Person years	Crude Incidence Rate per 10000 person years (95% CI)	No of incident cases	Total Person years	Crude Incidence Rate per 10000 person years (95% CI)	
Secondary Osteoporosis	No	262	7846.5	333.9 (295.83 to 376.89)	122	3853.4	316.60 (265.12 to 378.07)	
Secondary Osteoporosis	Yes	54	1506.2	358.51 (274.58 to 468.10)	30	775.4	386.89 (270.51 to 553.34)	
Previous Fracture	No	144	6832.0	210.77 (179.01 to 248.17)	63	3319.4	189.79 (148.26 to 242.95)	
	Yes	172	2520.8	682.32 (587.61 to 792.31)	89	1309.4	679.69 (552.18 to 836.64)	
	None	144	6832.0	210.77 (179.01 to 248.17)	63	3319.4	189.79 (148.26 to 242.95)	
Previous Fracture, detail	1 fracture	105	1919.6	546.99 (451.76 to 662.29)	52	1049.8	495.36 (377.47 to 650.07)	
	2-4 fractures	57	557.9	1021.62 (788.04 to 1324.45)	33	236.2	1397.28 (993.37 to 1965.44)	
	5+ fractures	10	43.2	2311.27 (1243.59 to 4295.60)	4	23.5	1701.81 (638.72 to 4534.31)	
Total		316	9352.8	337.87 (302.60 to 377.25)	152	4628.8	328.38 (280.11 to 384.96)	

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Supplementary Figure 1 Predicted and Observed risk by 10th of predicted risk for each risk prediction model in the derivation dataset.



Supplementary Figure2. Receiver Operating Characteristic curve for each model using the derivation dataset, with related Harrell's C-Index (analogous to the AUC).

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Section/Topic	Item		Checklist Item	Pa
Fitle and abstract	[1	Identify the study on developing and/or validating a multivariable prediction model, the	1
Title	1	D;V	target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size,	3
ntroduction				<u> </u>
			Explain the medical context (including whether diagnostic or prognostic) and rationale	
Background	3a	D;V	for developing or validating the multivariable prediction model, including references to	4
and objectives	26		Specify the objectives, including whether the study describes the development or	
	30	D, v	validation of the model or both.	
lethods	1	1	Describe the study design or source of data (e.g., randomized trial, cohort, or registry	
.	4a	D;V	data), separately for the development and validation data sets. if applicable.	
Source of data	4b	D:V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable,	
		2,1	end of follow-up.	
	5a	D;V	population) including number and location of centres.	
Participants	5b	D;V	Describe eligibility criteria for participants.	
	5c 🗸	D;V	Give details of treatments received, if relevant.	
	6a	D:V	Clearly define the outcome that is predicted by the prediction model, including how and	
Outcome	64		When assessed.	
	do	U;V	Report any actions to bind assessment of the outcome to be predicted.	
Brodictora	7a	D;V	model, including how and when they were measured.	
Predictors	7h	D·V	Report any actions to blind assessment of predictors for the outcome and other	
O a man l	.0	D, V	predictors.	
Sample size	8	D;V	Explain how the study size was arrived at.	
Missing data	9	D;V	imputation, multiple imputation) with details of any imputation method	
	10a	D	Describe how predictors were handled in the analyses	
	106		Specify type of model, all model-building procedures (including any predictor selection),	
Statistical	dui	U	and method for internal validation.	
analysis	10c	V	For validation, describe how the predictions were calculated.	6
methods	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare	6
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	6
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	
Development	12	V	For validation, identify any differences from the development data in setting, eligibility	
vs. validation	12	Ň	criteria, outcome, and predictors.	
Kesults		1	Departies the flow of participants through the study, including the number of participants	1
	13a	D·V	with and without the outcome and if applicable a summary of the follow-up time A	
	iou	0,1	diagram may be helpful.	
Participante			Describe the characteristics of the participants (basic demographics, clinical features,	
ranicipants	13b	D;V	available predictors), including the number of participants with missing data for	
			predictors and outcome.	
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome)	9
	14a	D	Specify the number of participants and outcome events in each analysis.	
Model	116		If done, report the unadjusted association between each candidate predictor and	
developinent	140	U	outcome.	
Model	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression	18
specification	15h	П	coefficients, and model intercept or baseline survival at a given time point).	
Model	100			
performance	16	D;V	Report performance measures (with CIs) for the prediction model.	12
Model-undating	17	V	If done, report the results from any model updating (i.e., model specification, model	10
	L.''		performance).	12
iscussion			Discuss any limitations of the study (such as nonrepresentative sample, few events per	
Limitations	18	D;V	predictor, missing data).	14
	19a	V	For validation, discuss the results with reference to performance in the development	
Interpretation		-	data, and any other validation data.	
	19b	D;V	from similar studies, and other relevant evidence	14
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	1
Other information		· ·		
Supplementary	21	D·V	Provide information about the availability of supplementary resources, such as study	18
information		5,*	protocol, Web calculator, and data sets.	10
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	2

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

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Does Bone Mineral Density Improve the Predictive Accuracy of Fracture Risk Assessment? A Prospective Cohort Study in Northern Denmark.

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Title

Does Bone Mineral Density Improve the Predictive Accuracy of Fracture Risk Assessment? A Prospective Cohort Study in Northern Denmark.

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Competing Interests

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

All authors have completed the ICMJE uniform disclosure form at <u>www.icmje.org/coi_disclosure.pdf</u> and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration

The lead author (Dr Dhiman) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical Approval

Ethics approval was given through the Region of North Jutland's from the Danish Data Protection Agency ("paraplyanmeldelse 2008-58-0028").

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Disclaimer

The views expressed are those of the author(s) and not necessarily those of the NIHR, the NHS or the Department of Health.

Patient Involvement

Patients were not involved in the development of this research question.

Data Sharing Statement

Data sharing: Technical appendix and statistical code is available from the corresponding author at paula.dhiman@nottingham.ac.uk. Due to restrictions by the Danish Data Protection Agency, data can only be shared on an aggregated level and by special permission.

Contributorship

Contributors: PD wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. PV and SA provided the AURORA dataset for analysis and linked patients to the National Patient Registry of Denmark, they also reviewed and revised the draft paper. NQ and TM provided clinical expertise, and reviewed and revised the draft paper.

Abstract:

Objective: To evaluate the added predictive accuracy of bone mineral density (BMD) to fracture risk assessment.

Design: Prospective cohort study using data between 01/01/2010 and 31/12/2012.

Setting: North Denmark Osteoporosis Clinic of referred patients presenting with at least one fracture risk factor to the referring doctor.

Participants: Patients aged 40-90 years; had BMD T-score recorded at the hip; and not taking osteoporotic preventing drugs for more than 1-year prior to baseline.

Main outcome measures: Incident diagnoses of osteoporotic fractures (hip, spine, forearm, humerus, and pelvis) were identified using the National Patient Registry of Denmark during 01/01/2012-01/01/2014. Cox regression was used to develop a fracture model based on predictors in the Fracture Risk Assessment Tool (FRAX®), with and without, binary and continuous BMD. Change in Harrell's C-Index and Reclassification tables were used to describe the added statistical value of BMD.

Results: Adjusting for predictors included in FRAX®, osteoporotic patients (T-score \leq -2.5) had 75% higher hazard of a fracture compared to patients with higher BMD (HR:1.75 (95% CI:1.28 to 2.38)). Forty-percent lower hazard was found per unit increase in continuous BMD T-score (HR:0.60 (95% CI:0.52 to 0.69)).

Accuracy improved marginally, and Harrell's C-Index increased by 1.2% when adding continuous BMD (0.76 to 0.77). Reclassification tables showed continuous BMD shifted 529 patients into different risk categories; 292 of these were reclassified correctly (57%; 95% CI:55% to 64%). Adding binary BMD however no improvement: Harrell's C-Index decreased by 0.6%.

Conclusions: Continuous bone mineral density marginally improves fracture risk assessment. Importantly, this was only found when using continuous BMD measurement for osteoporosis. It is suggested that future focus should be on evaluation of this risk factor using routinely collected data, and on the development of more clinically relevant methodology to assess the added value of a new risk factor

Article Summary

Strengths and Limitations:

- Addresses a research question recommended by The National Institute for Health and Care Excellence to investigate the added value of bone mineral density to fracture risk prediction.
- Investigates bone mineral density in both the commonly used, binary, and continuous • format.
- Presents changes in calibration, discrimination, and reclassification to describe the • added value of bone mineral density.
- Uses robustly collected data from Northern Denmark, with 3.2% missing data. •
- As data is from a North Danish population, with at least one fracture risk factor, this ralisabırıy . limits generalisability of the results.

Introduction

Osteoporosis causes over 8.9 million fractures worldwide, of which over 4.5 million occur in the USA and Europe, and account for 2.8 million disability adjusted life years (1). Further, 1.2 million disability adjusted life years are accounted for by hip fractures, which are projected to increase to 6 million by 2050 (2).

Given this burden, and treatment options for osteoporosis, identifying patients at risk of an osteoporotic fracture is high priority amongst health policymakers to reduce the risk of future fracture (3). Risk prediction tools have been developed to aid in the identification of patients at risk. For example, the Fracture Risk Assessment Tool (FRAX®) and QFracture® are commonly used to assess fracture risk in patients based on pre-defined risk factors.

Bone mineral density (BMD), a measurement used to aid diagnosis of osteoporosis, has also been identified as a fracture risk factor (4-7). Unlike some other fracture risk factors, treatment options (e.g. bisphosphonate medication) are available that reduces the fracture risk markedly when treatment is initiated based on low BMD.

English National guidelines (The National Institute for Health and Care Excellence (NICE)) for fracture risk assessment recommend treatment of osteoporosis to prevent fractures but have not included BMD as a mandatory risk factor for fracture risk prediction tools to incorporate (8). This is partly due to the lack of robust evidence and limited generalisability of current research, which has particularly focused on evaluating BMD in postmenopausal women evaluating the added value of BMD to existing fracture risk factors (5-7).

The National Institute of Clinical Health and Excellence also recognise this gap in the evidence and have recommended research to assess the added value of BMD as a risk factor in fracture risk assessment (9).

The aim of this study is to assess the value of BMD measurement in addition to the standard fracture risk factors used in the FRAX® risk model using a robustly collected prospective cohort.
Methods

This paper has been written in accordance to the TRIPOD checklist.

Patient Involvement

Patients were not involved in the development of this research question and were not involved in the design of this study.

Study Design and Data Source

A prospective cohort study was conducted using patients from the Aalborg University Hospital Record for Osteoporosis Risk Assessment (AURORA) dataset; patients were followed up using the National Patient Registry of Denmark.

The AURORA dataset consists of patients attending the Osteoporosis Clinic at Aalborg University Hospital after a referral from their primary care physician. A referral was offered to patients with at least one risk factor for osteoporosis (low BMI, previous fracture, parental hip fracture, smoking status, alcohol consumption, glucocorticoid use, rheumatoid arthritis, and secondary osteoporosis) or if they were aged 80 years and above. Further detail of the data collection has been described elsewhere (10). The Danish National Patient Registry which collects inpatient and outpatient data from all Danish hospitals, was linked to the AURORA dataset through unique patient identifiers

Ethics approval was given through the Region of North Jutland's from the Danish Data Protection Agency ("paraplyanmeldelse 2008-58-0028").

Cohort selection

Data collection for AURORA began 1st January 2010 and was collected for 3 years (up to 31st December 2012). Patients were included if they were aged 40-90 years; had a BMD T-score at the hip; and were not taking any osteoporotic preventing drugs or any bone sparing drugs for more than one year prior to baseline.

Primary Outcome

The primary outcome measure was an incident osteoporotic fracture during follow up (01/01/2012 to 01/01/2014); defined as a diagnosis of a fracture at the hip, spine, forearm, humerus, and pelvis. Fractures at these sites resulting from traffic, work, and sports related accidents were excluded from the study. Relevant fractures were identified in the Danish National Patient Registry, using the International Statistical Classification of Diseases, 10th Version codes (ICD-10 codes), which was developed using recognised database methodology for each fracture (11).

Fracture risk factors

Fracture risk factors, used in the FRAX® risk prediction model, were extracted at baseline. They were: age; gender; height (m); weight (kg); previous fracture; parental history of hip fracture, current smoking status; current alcohol consumption; glucocorticoid use (currently exposed for 3+ months); rheumatoid arthritis; and secondary osteoporosis (includes type I diabetes; osteogenesis imperfecta in adults; untreated, long standing hyperthyroidism;

hypogonadism; premature menopause (<45 years); chronic malnutrition; malabsorption; and chronic liver disease).

Bone Mineral Density

DXA scans were performed by trained technicians using Hologic Discovery A (Bedford, MA, USA). A daily QC programme was in place and in vivo CV using repositioning of patients was <1%. Total hip BMD was used as region of interest. Bone mineral density was added to the fracture risk prediction model twice, firstly, as a continuously measured T-score value, and secondly, as a binary risk factor, dichotomised at/above T-score threshold for osteoporosis and below threshold, -2.5 in T-score (manufacturers' normal range using normal material from T Kelly et al (12)) based on World Health Organisation (WHO) classifications (13). Calculated T-scores were gender specific.

Statistical Analysis

A complete case analysis was performed on the data; 3.2% of data was missing. The AURORA dataset was split into two using recognised methodology (14); where a random number was assigned to patients and based on a cut off, two-thirds was used to derive the risk models, and the remaining third was used to validate them.

Model derivation

Three Cox proportional hazards models were developed for the primary outcome, using a complete case analysis on the derivation dataset:

- Model 1. Standard fracture risk factors only (without BMD)
- Model 2. Standard fracture risk factors (with binary BMD)
- Model 3. Standard fracture risk factors (with continuous BMD)

Graphical methods were used (log-log plots) to assess the proportional hazards assumption, and risk factors violating this assumption were added to the model as a time varying covariate.

Recognised methodology used in research studies was used to build the 3 risk prediction models (15, 16); the Kaplan Meier method was used to obtain 4-year fracture risk estimates for patients. Further detail on the conversion of the Cox proportional hazards models to risk prediction models has been provided in Supplementary Table 1.

Validation of Models

Four-year fracture risk was calculated from each model and the predictive performance of each risk prediction model was assessed by measures describing calibration, discrimination, and reclassification. These metrics were assessed using the validation cohort.

Calibration measures how well the predicted risk agrees with observed risk in the data. It plots the mean predicted and observed risk of fracture for each decile of predicted risk. The observed risk of fracture was derived from the 4 year Kaplan-Meier estimate. Good calibration indicates the predicted risk is close to the observed risk of the outcome.

Discrimination measures how well the risk prediction model differentiates between patients who have or have not observed the event in the study. This was quantified by the area under

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the receiver operating characteristic (ROC) curve (AUC), given by Harrell's C-Index with higher values indicating better discrimination.

Reclassification tables (17) measures movement between risk categories when adding a new risk factor. Threshold for treatment at 4 years was set at a fracture risk level of 8.5%; to be comparable to the treatment threshold of 20% at 10 years. This was presented by the total percent of patients reclassified (incorrectly and correctly), and also the Net Reclassification Index (NRI) (18, 19). The NRI gives the net calculation of the changes in the right direction and a higher NRI indicates a better reclassifying model.

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All analyses were carried out using Stata (version 12) (20).

Results

Characteristics of the data

The AURORA collected data on 7,912 patients; 1,795 patients were excluded comprising, 440 not aged between 40-90 years at baseline; 156 not having a recorded T-score value for the total hip at baseline; and 1,199 patients were taking anti-osteoporotic drug therapy for more than one year prior to baseline.

The study sample consisted of 6,117 patients; predominantly female (79.6%), and patients with a mean age of 62.9 (SD: 10.9) years. Two-thirds of this sample (n=4,093) was used for the derivation dataset and one-third (n=2,094) was used for the validation dataset. Table 1 presents the baseline characteristics of the study by derivation and validation dataset, and shows little difference between the datasets.

Patients in the derivation dataset had a median follow up time of 2.30 years [1.57, 2.99], and observed 318 (7.8%) osteoporotic fractures during follow up. Of these, 316 fractures were eligible for the analysis (2 patients had a fractures on or prior to baseline and were excluded). Patients contributed 9352.8 person years of observation, giving a total incidence rate of 337.87 per 10,000 person years (95% CI:302.60 to 377.25).

Fractures during follow up were predominantly found in the forearm (27.0%) and hip (17.9%). Higher fracture incidence rates were found in patients classed as osteoporotic, based on their T-score at both the total hip (809.73 per 10,000 person years (95% CI:641.68 to 1021.78)) and spine (L1-L4) (553.59 per 10,000 person years (95% CI:462.55 to 662.55)) (Supplementary Table 2).

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Chanastanistia			Derivation		Validation	
Characteristic			(11-4,) No	093) %	(II-2,) No	924) %
Gender	Female		3 266	79.8	1 602	79.2
	Male		827	20.2	422	20.8
Osteoporotic (Hip DXA)	No		3.683	90.0	1.820	89.9
	Yes		410	10.0	204	10.1
Osteoporotic Status (based on	Normal		1,886	46.1	927	45.8
UK guidelines)	Osteopenic		1,797	43.9	893	44.1
	Osteoporotic		410	10.0	204	10.1
Previous Fracture	No		2,935	71.7	1,423	70.3
	Yes		1,158	28.3	601	29.7
No of Previous Fractures	None		2,935	71.7	1,423	70.3
	1 fracture		862	21.1	467	23.1
	2-4 fractures		270	6.6	122	6.0
	5+ fractures		26	0.6	12	0.6
Parental History of Hip Fracture	No		2,755	67.3	1,359	67.1
	Yes		1,338	32.7	665	32.9
Current Smoking Status	other (non/ex)		3,182	77.7	1,529	75.5
C	smoker		911	22.3	495	24.5
Alcohol Consumption	≤3 units per day		3,875	94.7	1,923	95.0
-	>3 units per day		218	5.3	101	5.0
Glucocorticoid Use	No		3,577	87.4	1,741	86.0
	Yes		516	12.6	283	14.0
Rheumatoid Arthritis	No		3,686	90.1	1,801	88.0
	Yes		407	9.9	223	11.0
Other Bone Affecting Disease	No		2,382	58.2	1,139	56.3
	Yes		1,711	41.8	885	43.7
Secondary Osteoporosis	No		3,438	84.0	1,689	83.5
	Yes		655	16.0	335	16.6
	By disease					
	Type 1 diabetes	No	4,010	98.0	1,981	97.9
		Yes	83	2.0	43	2.1
	Osteogenesis	No	4,093	100	2,024	100
		Yes	0	0	0	0
	Hyperthyroidism	No	4,089	99.9	2,023	99.9
		Yes	4	0.1	1	0.1
	Malnutrition	No	4,090	99.9	2,023	99.9
		Yes	3	0.1	1	0.1
	Chronic Liver Disease	No	4,006	97.9	1,979	97.8
		Yes	87	2.1	45	2.2
	Menopause (Females only)**	No	853	26.1	405	25.3

 Table 1. Baseline characteristics of the derivation and validation datasets, including missing data.

	Premature Menopause (<45 years)***	No	1,904	78.9	941	78.6
		Yes	509	21.1	256	21.4
			Mean	SD	Mean	SD
Age (years)			62.9	10.9	63.0	11.0
Weight (kg)			72.1	15.5	72.2	15.9
	Missing		47	1.2	12	0.6
Height (m)			1.7	0.1	1.7	0.1
	Missing		131	3.2	61	3.0
BMI			26.4	5.0	26.4	5.1
	Missing		135	3.3	63	3.1
Hip DXA T-score			-11	11	-12	11

*out of patients with a fracture

**proportion out of respective number of females

***proportion out of respective number of females with menopause

Model development

The unadjusted analysis showed statistically significant association between BMD (continuous and binary) and osteoporotic fracture (p<0.001). Significant associations with fracture were also found with age (p<0.001), previous fracture (p<0.001), BMI (p=0.03), and gender (p=0.05). Further, a time-varying effect was found in patients with a previous fracture; hazard of a subsequent fracture was highest in the first year during follow up and decreased per year of follow up (p<0.001).

The adjusted analysis is presented in Table 2. Model 1 showed that of the standard risk factors, age and previous fracture were significantly associated with fracture; hazard of fracture increased by 2% per year increase in age (HR=1.02; 95% CI: 1.01 to 1.04); and increased almost 5 fold in patients with a previous fracture at time 0 years (HR=4.88; 95% CI: 3.37 to 7.08).

Hazard of fracture increased by 75% for patients classed as osteoporotic by their BMD score (Model 2, HR=1.75; 95% CI: 1.28 to 2.38). Hazard of fracture also decreased by 40% per SD improvement in BMD T-score (Model 3, HR=0.60; 95% CI: 0.52 to 0.69).

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Table 2. Multivariate analysis for osteoporotic fracture in the derivation cohort. Data are adjusted hazard ratios and 95% confidence intervals.

		Adju	usted Hazard Ratio (95%	% CI)
Risk Factor		Model 1: Standard Risk Factors only	Model 2: Standard Risk Factors + BMD (categorical)	Model 3: Standard Risk Factors + BMD (continuous)
Age (years)		1.02 (1.01 to 1.04)	1.02 (1.01 to 1.03)	1.01 (1.00 to 1.02)
Gender	Female	Ref	Ref	Ref
Gender	Male	0.75 (0.54 to 1.04)	0.80 (0.57 to 1.10)	0.85 (0.61 to 1.18)
BMI		0.98 (0.95 to 1.00)	0.99 (0.96 to 1.01)	1.03 (1.00 to 1.05)
Dravious Fracture	No	Ref	Ref	Ref
Flevious Flacture	Yes (time = 0 years)	4.88 (3.37 to 7.08)	4.67 (3.21 to 6.78)	4.02 (2.76 to 5.84)
Demonstral History of His Erecture	No	Ref	Ref	Ref
Parental History of Hip Flacture	Yes	1.08 (0.83 to 1.40)	1.10 (0.85 to 1.42)	1.11 (0.85 to 1.43)
Comont Smaller	No	Ref	Ref	Ref
Current Smoker	Yes	1.12 (0.85 to 1.47)	1.08 (0.82 to 1.42)	1.02 (0.77 to 1.34)
Alashal Communition (>2 units/day)	No	Ref	Ref	Ref
Alconol Consumption (>3 units/day)	Yes	1.41 (0.90 to 2.21)	1.44 (0.92 to 2.25)	1.04 (0.72 to 1.49)
	No	Ref	Ref	Ref
Glucocorticold Use	Yes	1.08 (0.75 to 1.55)	1.05 (0.73 to 1.51)	1.46 (0.93 to 2.28)
Dhoumotoid Anthuitig	No	Ref	Ref	Ref
Kneumatoid Artifitis	Yes	1.10 (0.73 to 1.65)	1.09 (0.72 to 1.64)	1.12 (0.74 to 1.68)
Secondamy Osteonomosia	No	Ref	Ref	Ref
Secondary Osteoporosis	Yes	0.99 (0.73 to 1.35)	0.97 (0.71 to 1.32)	0.91 (0.67 to 1.24)
Osteoporotic	No	Ref	Ref	Ref
	Yes	-	1.75 (1.28 to 2.38)	-
Hip DXA T-score (SD)		-	-	0.60 (0.52 to 0.69)
Previous Fracture (TVC [*])		0.64 (0.49 to 0.83)	0.64 (0.49 to 0.83)	0.64 (0.50 to 0.84)

*TVC = time varying covariate, value is interaction effect and 95% CI.

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Model Validation

The 4-year predicted risk of fracture was calculated for all patients in the validation dataset; this was compared to the observed fracture outcome within the 4 year follow up.

Calibration and Discrimination

Calibration plots suggested some improvement when adding BMD measurement; particularly when including continuous BMD T-score measurement (Model 3; Supplementary Figure 1).

The largest change in discrimination was found when adding continuous BMD measurement to standard risk factors; Harrell's C-Index increased by 1.17% (Table 3). However, binary BMD measurement, as a measure for osteoporotic patients, was found to reduce Harrell's C-Index by -0.65%.

Table 3. Harrell's C-Index for Model 1, 2, 3, 4, and 5.

Model	Harrell's C-Index	Change in Harrell's C-Index (% change)*
Model 1 : Standard fracture risk factors only (without BMD)	0.764 (0.718 to 0.810)	-
Model 2 : Standard fracture risk factors only (with binary BMD)	0.759 (0.712 to 0.806)	-0.005 (-0.65%)
Model 3: Standard fracture risk factors	0.773 (0.732 to 0.814)	0.009 (1.17%)
hange is measures against Model 1.		

Reclassification

Reclassification tables suggested that adding continuous BMD measurement improved classification of patients into their correct risk categories. This was not found when adding binary BMD. Table 4 presents the reclassification table for Model 1 (standard fracture risk factors only) and Model 3 (standard risk factors with continuous BMD), using the 8.5% prespecified risk threshold.

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			Model 3: continuo	SRF with us BMD		
			<8.5%	≥8.5%	Total	Total No.(%) Reclassified
		No	391	227		
		%	63.3%	36.7%		
Model 1: SRF	<8.5%	No. Events	5	9	618	227 (36.7%)
without BMD		No. Non events	386	218		
	C	Observed Event Rate	1.3%	4.0%		
	•	No	302	1,040		
		%	22.5%	77.5%		
	≥8.5%	No. Events	10	121	1,342	302 (22.5%)
		No. Non events	292	919		
		Observed Event Rate	3.3%	11.6%		
	Total		693	1,267	1,960	529 (27.0%)

Table 4. Risk Reclassification Table comparing Model 1 (standard fracture risk factors alone)to Model 3 (standard fracture risk factors with continuous BMD measurement), using a clinical8.5% risk cut off.

Of the 1,960 patients in the validation dataset, 27% (n=529) were reclassified into a different risk category when including continuous BMD into fracture risk prediction. Two percent (9/529) were found to be reclassified correctly into a higher risk group and 55% (292/529) were reclassified correctly into a lower risk group; indicating 22% (292/1342) of patients at high risk in Model 1, not accounting for BMD measurement, were no longer at high risk. The net reclassification improvement when adding continuous BMD to standard risk factors, was 0.03, which resulted from increased specificity (non-event NRI = 4%) and decreased sensitivity (event NRI: -1%) from Model 1 (Table 5).

Table 5. Summary of Net Reclassification Index (NRI) and Integrated Discrimination Index (IDI) for all comparisons between developed fracture risk prediction models.

Comparison	Event NRI	Non-Event NRI	Overall NRI
Model 1 vs. Model 2	-3.45%	2.09%	-0.01
Model 1 vs. Model 3	-0.69%	4.08%	0.03

Discussion

Summary of Findings

Bone mineral density showed significant association with fracture risk with a 40% decrease for each SD rise in BMD. However, this resulted in small improvements in calibration, discrimination, and reclassification. Despite the limited improvement was found of 1% in discrimination when adding continuous BMD, reclassification tables showed 57% of reclassified patients moving into their correct risk group through improved specificity.

Importantly no improvement was found when adding BMD in a binary format. Our findings are consistent with and corroborate with current literature (7, 21). Specifically, a study conducted in the Netherlands with 4 year follow up, investigating the added value of BMD for hip fractures risk found modest improvement in predictability (21). Further, a more recent study also indicated limited added value of BMD to fracture risk prediction (7).

Strengths and Limitations

Answering Evidence gap

To our knowledge, this is the first study to investigate the added value of BMD in a binary and continuous format, to standard fracture risk factors. It helps inform the NICE research recommendation to assess the added value of BMD to routine fracture risk assessment in primary care (22). It further highlights that the more commonly used for treatment decision making, binary format of BMD resulted in a loss of predictability in fracture risk prediction; based on comparable measures for discrimination and reclassification

Robustness of Data

The prospective cohort was well populated with key standard risk factors recorded: BMI, smoking status and alcohol consumption, and personal and parental fracture history. Other than 3.2% of missing data for BMI, in 6,117 patients, complete data was collected for all risk factors (including BMD T-score recorded at the total hip). Further, the cohort was linked to a national robust electronic health records. This Danish National Patient Registry allowed for outcome fracture to be identified and also provided data on the mechanism for the fracture; this helped more accurately phenotype osteoporotic fractures.

Generalisability

The generalisability is affected in a few ways. Firstly, the findings are based on a Danish cohort. Secondly, AURORA data was collected from patients who presented to their doctor with at least one fracture risk factor and were referred to the osteoporosis clinic; this led to a biased study sample with a higher risk of a fracture and increased age. This could overestimate fracture risk amongst patients in a primary care setting.

Methodology

Due to the increased age of the sample, death becomes a competing risk. However, information on death was not collected and could not be retrieved. This limited the analysis of the data as competing risks could not be accounted for which may again lead to an overestimation of fracture risk (23). However, as an independent study primarily assessing the added value of BMD through deriving and validating the fracture risk prediction models,

this bias would be present in both analyses to compare derived risk models with and without BMD measurement.

The FRAX risk algorithm has not yet been published, therefore FRAX estimates could not be directly calculated for the cohort. Instead, the FRAX risk model was recalibrated on the dataset with and without BMD added. Further, fracture outcomes in this study included pelvic fractures which are increasingly recognised as low trauma fragility fractures [(24)], and used BMD taken at the total hip instead of at the femur neck as it is the gold standard in Denmark (25).

Internal validation was performed to validate the derived risk prediction models. This may lead to over optimistic results of the performance of the risk models (14). To account for this limitation, a commonly practised method which randomly assigns patients to the derivation and validation datasets was used; further, a similar 1:2 ratio was also used to split the data (26-28).

The study had a 4 year follow up which is shorter than other recognised risk models. To account for this, we adapted the 20% clinical risk threshold for 10 year fracture estimates to 8.5% for 4 year fracture estimates, assuming that risk is constant over time (29, 30).

Traditional methodology assessing the added value to risk factors to existing risk prediction models are criticised to be insensitive to change, to lack interpretability (31-34). This was shown when finding a 1% change in Harrell's C-Index and overlapping confidence intervals between models, limiting the interpretability of results. Reclassification analysis was thus also used to provide more clinically interpretable results.

Clinical implications

The most notable clinical implication is the more routine use of BMD measurement for fracture risk assessment. Further, evidence suggests continuous BMD adds better predictability compared to the binary format.

Future Research

Further research is recommended to evaluate the added value of BMD to fracture risk prediction; in particular in addition to QFracture risk factors and using primary care routinely collected data. However, a brief interrogation into the Clinical Practice Research Datalink, a routinely collected UK primary care database, showed poor availability of BMD measurement in patient records, and thus, strong limitations to potential analyses. Less than 1% of patients had BMD recorded from a sample of 60,658 patients aged 40-90; not on any osteoporotic treatment; and with complete data for age, gender, BMI, smoking status, and alcohol consumption. Thus, prior to UK analysis, BMD recording in primary care databases needs to improve.

Methodologically, as well as assessing the added value of BMD to standard risk factors, we should also explore the option to replace existing fracture risk factors with the BMD measurement; this has rarely been explored in the literature but should be considered in future analyses. We also recommend research to investigate the added value of BMD in a potentially more natural, 3 group format of BMD (osteopenic, normal, osteoporotic).

In addition, further research is recommended to develop current methodology used to assess the added value of BMD to provide more clinically relevant results, such as cost implications; and to allow for better comparability between new risk factors with respect to their added value, thus improving decision making.

Conclusion

Continuous BMD marginally improves fracture risk assessment. Importantly, this was only found when using continuous BMD measurement for osteoporosis. It seems that prediction models for fragility fracture risk may be improved only marginally, using present risk factor assessment and evaluations. It is suggested that future focus should be on additional risk factors and on the development of more clinically relevant methodology to assess the added value of a new risk factor.

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Beta coefficients from each Cox regression model were used to create each fracture risk prediction model.

Once all 5 models were finalised, their beta coefficients were used to create 5 risk prediction models and calculate risk of fracture for each patient, using the following general equation:

$$\widehat{risk} = 1 - S_0(t)^{exp(\sum_{i=1}^p \beta_i X_i - \sum_{i=1}^p \beta_i \overline{X}_i)}$$

Where $S_0(t)$ is the baseline survival rate at follow up time, t(for this example, a follow up time of 10 years will be used); beta (β_i) are the regression coefficients for each included risk factor in the model (i); X_i is the observed data value for each risk factor; \overline{X}_i is the corresponding mean for each risk factor; and \mathbf{p} is the total number of risk factors included in the model. Table A1 shows the formula for each risk prediction model explicitly.

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$1.585278*\text{mean previous fracture}+0.0762559*\text{mean parental hip fracture}+ 0.1138883*\text{mean smoking status}+0.0773898*\text{mean glucocorticoid use}+ 0.3465287*\text{mean alcohol consumption}+0.0936966*\text{mean rheumatoid arthritis} -0.0069432*\text{mean secondary osteoporosis}+-0.4535108*\text{mean (previous fracture}) where \sum_{t=1}^{p} \beta_t X_t = 0.0186827*age+-0.228784*gender+-0.0113651*BMI+1.540559*previous fracture 0.092011*parental hip fracture+0.0732564*smoking status+0.0508706*gluco-0.3649544*alcohol consumption+0.0854353*rheumatoid arthritis+-0.034688 osteoporosis+0.5568944*osteoporosis+-0.4481145*(previous fracture*time) where \sum_{t=1}^{p} \beta_t \overline{X}_t = 0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+1.540559*mean previous fracture+0.092011*mean parental hip fracture+0.0732564*mean gender+-0.013651*mean BMI+1.540559*mean age+-0.228784*mean gender+-0.0113651*mean BMI+1.540559*mean previous fracture+0.092011*mean parental hip fracture+0.0732564*mean age+-0.228784*mean gender+-0.0113651*mean BMI+1.540559*mean previous fracture+0.092011*mean parental hip fracture+0.0732564*mean age+-0.228784*mean gender+-0.0113651*mean BMI+1.540559*mean previous fracture+0.092011*mean parental hip fracture+0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis-0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+$		0.0237745*mean age+-0.2826461*mean gender+-0.0225011*mean BMI+
$0.1138883* \text{mean smoking status} + 0.0773898* \text{mean glucocorticoid use} + 0.3465287* \text{mean alcohol consumption} + 0.0936966* \text{mean rheumatoid arthritis} - 0.0069432* \text{mean secondary osteoporosis} + -0.4535108* \text{mean (previous fracture} where \sum_{i=1}^{p} \beta_i X_i = 0.0186827* \text{age} + -0.228784* \text{gender} + -0.0113651* \text{BMI} + 1.540559* \text{previous fracture} + 0.092011* \text{parental hip fracture} + 0.0732564* \text{smoking status} + 0.0508706* \text{gluco} + 0.3649544* \text{alcohol consumption} + 0.0854353* \text{rheumatoid arthritis} + -0.034688 \text{osteoporosis} + 0.5568944* \text{osteoporosis} + -0.4481145* (\text{previous fracture}* \text{time}) where \sum_{i=1}^{p} \beta_i \overline{X}_i = 0.0186827* \text{mean age} + -0.228784* \text{mean gender} + -0.0113651* \text{mean BMI} + 1.540559* \text{mean previous fracture} + 0.0732564* \text{mean age} + -0.228784* \text{mean gender} + -0.0113651* \text{mean BMI} + 1.540559* \text{mean smoking status} + 0.0508706* \text{mean glucocorticoid use} + 0.0732564* \text{mean smoking status} + 0.0508706* \text{mean glucocorticoid use} + 0.3649544* \text{mean alcohol consumption} + 0.0854353* \text{mean rheumatoid arthritis} - 0.0346885* \text{mean secondary osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.0854353* \text{mean rheumatoid arthritis} - 0.0346885* \text{mean secondary osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.0508706* \text{mean rheumatoid arthritis} - 0.0346885* \text{mean secondary osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.0508706* \text{mean rheumatoid arthritis} - 0.0346885* \text{mean secondary osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.0508706* \text{mean rheumatoid arthritis} - 0.0346885* \text{mean secondary osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.0508706* \text{mean rheumatoid arthritis} - 0.0346885* \text{mean secondary osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.0508706* \text{mean rheumatoid arthritis} - 0.0346885* \text{mean secondary osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.0508706* \text{mean secondary osteoporosis} + 0.0508$		1.585278*mean previous fracture+0.0762559*mean parental hip fracture+
$0.3465287*\text{mean alcohol consumption}+0.0936966*\text{mean rheumatoid arthritis} -0.0069432*\text{mean secondary osteoporosis}+-0.4535108*\text{mean (previous fracture)} where \sum_{i=1}^{p} \beta_i X_i =0.0186827*age+-0.228784*gender+-0.0113651*BMI+1.540559*previous fracture + 0.092011*parental hip fracture+0.0732564*smoking status+0.0508706*glucore + 0.3649544*alcohol consumption+0.0854353*rheumatoid arthritis+-0.034688 + 0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+ 1.540559*mean previous fracture+0.092011*mean parental hip fracture+ 0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+ 0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis+ -0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+0.5568944*mean osteoporosis+ 0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+0.5568944*mea$		0.1138883*mean smoking status+0.0773898*mean glucocorticoid use+
$-0.0069432*\text{mean secondary osteoporosis}+-0.4535108*\text{mean (previous fracture)}$ where $\sum_{i=1}^{p} \beta_i X_i =$ 0.0186827*age+-0.228784*gender+-0.0113651*BMI+1.540559*previous fracture) Model 2 0.092011*parental hip fracture+0.0732564*smoking status+0.0508706*glucoe 0.3649544*alcohol consumption+0.0854353*rheumatoid arthritis+ -0.034688 osteoporosis+0.5568944*osteoporosis+-0.4481145*(previous fracture*time) where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ 0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+ 1.540559*mean previous fracture+0.092011*mean parental hip fracture+ 0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+ 0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+		0.3465287*mean alcohol consumption+0.0936966*mean rheumatoid arthritis+
where $\sum_{i=1}^{p} \beta_i X_i =$ 0.0186827*age+-0.228784*gender+-0.0113651*BMI+1.540559*previous fractional fracture in the interval of the int		-0.0069432*mean secondary osteoporosis+-0.4535108*mean (previous fracture
Model 2 $0.0186827*age+-0.228784*gender+-0.0113651*BMI+1.540559*previous fractionModel 20.092011*parental hip fracture+0.0732564*smoking status+0.0508706*glucos0.3649544*alcohol consumption+0.0854353*rheumatoid arthritis+ -0.034688osteoporosis+0.5568944*osteoporosis+-0.4481145*(previous fracture*time)where \sum_{i=1}^{p} \beta_i \overline{X}_i =0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+1.540559*mean previous fracture+0.092011*mean parental hip fracture+0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+$		where $\sum_{i=1}^{p} \beta_i X_i =$
Model 2 $0.092011*$ parental hip fracture+ $0.0732564*$ smoking status+ $0.0508706*$ gluco $0.3649544*$ alcohol consumption+ $0.0854353*$ rheumatoid arthritis+ - 0.034688 osteoporosis+ $0.5568944*$ osteoporosis+- $0.4481145*$ (previous fracture*time) where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ $0.0186827*$ mean age+- $0.228784*$ mean gender+- $0.0113651*$ mean BMI+ $1.540559*$ mean previous fracture+ $0.092011*$ mean parental hip fracture+ $0.0732564*$ mean smoking status+ $0.0508706*$ mean glucocorticoid use+ $0.3649544*$ mean alcohol consumption+ $0.0854353*$ mean rheumatoid arthritis- - $0.0346885*$ mean secondary osteoporosis+ $0.5568944*$ mean osteoporosis+		0.0186827*age+-0.228784*gender+-0.0113651*BMI+1.540559*previous fracto
0.3649544*alcohol consumption+0.0854353*rheumatoid arthritis+ -0.034688 osteoporosis+0.5568944*osteoporosis+-0.4481145*(previous fracture*time) where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ 0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+ 1.540559*mean previous fracture+0.092011*mean parental hip fracture+ 0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+ 0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis- -0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+	Model 2	0.092011*parental hip fracture+0.0732564*smoking status+0.0508706*glucocc
osteoporosis+0.5568944*osteoporosis+-0.4481145*(previous fracture*time) where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ 0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+ 1.540559*mean previous fracture+0.092011*mean parental hip fracture+ 0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+ 0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis- -0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+		0.3649544*alcohol consumption+0.0854353*rheumatoid arthritis+ -0.0346885*
where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ 0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+ 1.540559*mean previous fracture+0.092011*mean parental hip fracture+ 0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+ 0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis- -0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+		osteoporosis+0.5568944*osteoporosis+-0.4481145*(previous fracture*time)
0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+ 1.540559*mean previous fracture+0.092011*mean parental hip fracture+ 0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+ 0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis- -0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+		where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$
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0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis- -0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+		0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+
-0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+		0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis+
		-0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+
-0.4481145*mean (previous fracture*time)		-0.4481145*mean (previous fracture*time)

cont.	Equation
cont	
	where $\sum_{i=1}^{i} \beta_i X_i =$
	0.0071931*age+-0.1615582*gender+0.0268478*BMI+1.39069*previous fracture+
	0.1000272*parental hip fracture+0.0192416*smoking status+0.0374944*glucocorticoid use
	0.3774416*alcohol consumption+0.1097646*rheumatoid arthritis+ -0.0932063*secondary
	osteoporosis+-0.5110986*t-score+-0.4404955*(previous fracture*time)
Model 3	where $\sum_{i=1}^{P} \beta_i X_i =$
	0.0071931*mean age+-0.1615582*mean gender+0.0268478*mean BMI+
	1.39069*mean previous fracture+0.1000272*mean parental hip fracture+
	0.0192416*mean smoking status+0.0374944*mean glucocorticoid use+
	0.3774416*mean alcohol consumption+0.1097646*mean rheumatoid arthritis+
	-0.0932063*mean secondary osteoporosis+-0.5110986*mean t-score+
	-0.4404955*mean (previous fracture*time)

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	No of incident	Total	Crude Incidence Rate per	No of	Tot	Curde Incidence Dote
	cases	years	10000 person years (95% CI)	incident cases		10000 person years (9 CI)
40-49	17	1169.9	145.31 (90.33 to 233.74)	12	lated	215.15 (122.19 to 378.
50-59	70	2534.7	276.17 (218.49 to 349.07)	33	to te	251.71 (178.95 to 354.
60-69	93	3062.9	303.63 (247.79 to 372.06)	42	uperi xtan	288.87 (213.48 to 390.
70-79	83	1906.0	435.46 (351.17 to 539.98)	49	d dan d dan	511.11 (386.29 to 676.
80-89	52	652.7	796.75 (607.13 to 1045.59)	16		460.56 (282.15 to 751)
90-99	1	26.6	376.51 (53.04 to 2672.85)	-	ning,	-
No	245	8475.9	289.05 (255.03 to 327.61)	123	<u>A</u> 16 <mark>39</mark> 1	295.31 (247.48 to 352.
Yes	71	876.8	809.73 (641.68 to 1021.78)	29		625.28 (434.52 to 899)
No	191	7025.8	271.86 (235.91 to 313.28)	111	g a 47 5 6	319.37 (265.16 to 384
Yes	119	2149.6	553.59 (462.55 to 662.55)	39		358.08 (261.63 to 490.
Female	266	7417.5	358.61 (318.01 to 404.40)	129		350.56 (295.00 to 416.
Male	50	1935.3	258.36 (195.82 to 340.88)	23	echno	242.36 (161.05 to 364.
No	220	6281.5	350.24 (306.88 to 399.71)	118	2010827	379.58 (316.92 to 454.
Yes	96	3071.3	312.57 (255.90 to 381.79)	34	.1520-2	223.66 (159.81 to 313
	40-49 50-59 60-69 70-79 80-89 90-99 No Yes No Yes Female Male No Yes	40-49 17 50-59 70 60-69 93 70-79 83 80-89 52 90-99 1 No 245 Yes 71 No 191 Yes 119 Female 266 Male 50 No 220 Yes 96	40-49171109.950-59702534.760-69933062.970-79831906.080-8952652.790-99126.6No2458475.9Yes71876.8No1917025.8Yes1192149.6Female2667417.5Male501935.3No2206281.5Yes963071.3	40-49171105.9143.31 (90.33 to 233.74)50-59702534.7276.17 (218.49 to 349.07)60-69933062.9303.63 (247.79 to 372.06)70-79831906.0435.46 (351.17 to 539.98)80-8952652.7796.75 (607.13 to 1045.59)90-99126.6376.51 (53.04 to 2672.85)No2458475.9289.05 (255.03 to 327.61)Yes71876.8809.73 (641.68 to 1021.78)No1917025.8271.86 (235.91 to 313.28)Yes1192149.6553.59 (462.55 to 662.55)Female2667417.5358.61 (318.01 to 404.40)Male501935.3258.36 (195.82 to 340.88)No2206281.5350.24 (306.88 to 399.71)Yes963071.3312.57 (255.90 to 381.79)	40-49171105.9143.31 (90.33 to 233.74)1250-59702534.7276.17 (218.49 to 349.07)3360-69933062.9303.63 (247.79 to 372.06)4270-79831906.0435.46 (351.17 to 539.98)4980-8952652.7796.75 (607.13 to 1045.59)1690-99126.6376.51 (53.04 to 2672.85)-No2458475.9289.05 (255.03 to 327.61)123Yes71876.8809.73 (641.68 to 1021.78)29No1917025.8271.86 (235.91 to 313.28)111Yes1192149.6553.59 (462.55 to 662.55)39Female2667417.5358.61 (318.01 to 404.40)129Male501935.3258.36 (195.82 to 340.88)23No2206281.5350.24 (306.88 to 399.71)118Yes963071.3312.57 (255.90 to 381.79)34	40-49171109.9143.31 (90.33 to 233.74)12aray to50-59702534.7276.17 (218.49 to 349.07)3360-69933062.9303.63 (247.79 to 372.06)4270-79831906.0435.46 (351.17 to 539.98)4980-8952652.7796.75 (607.13 to 1045.59)1690-99126.6376.51 (53.04 to 2672.85)-No2458475.9289.05 (255.03 to 327.61)123Yes71876.8809.73 (641.68 to 1021.78)29No1917025.8271.86 (235.91 to 313.28)111Yes1192149.6553.59 (462.55 to 662.55)39Female2667417.5358.61 (318.01 to 404.40)129Male501935.3258.36 (195.82 to 340.88)23No2206281.5350.24 (306.88 to 399.71)11891067Yes963071.3312.57 (255.90 to 381.79)34152.92

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			D	Derivation		8898 clud	alidation
Risk Factor cont.		No of incident cases	Total Person years	Crude Incidence Rate per 10000 person years (95% CI)	No of incident cases	area and a construction of the construction of	Crude Incidence Rate per 10000 person years (95% CI)
Current Smoker	No	240	7279.1	329.71 (290.53 to 374.18)	103		293.19 (241.70 to 355.65)
	Yes	76	2073.7	366.5 (292.71 to 458.90)	49		439.16 (331.91 to 581.07)
Alcohol Consumption	No	293	8875.9	330.11 (294.39 to 370.15)	140	to te S	318.2 (269.63 to 375.53)
more than 3 units per day	Yes	23	476.9	482.33 (320.52 to 725.83)	12	oade uperi xt'anc	523.66 (297.39 to 922.09)
Glucocorticoid Use (3	No	279	8184.5	340.89 (303.15 to 383.33)	132		330.57 (278.73 to 392.06)
months)	Yes	37	1168.3	316.7 (229.47 to 437.11)	20	a min	314.57 (202.95 to 487.59)
Menopause	No	68	1962.8	346.44 (273.15 to 439.39)	29	<u>بو</u> 28	312.19 (216.94 to 449.24)
	Yes	198	5454.7	362.99 (315.79 to 417.24)	100	A Hrs	363.52 (298.82 to 442.23)
Premature Menopause	No	280	8175.4	342.49 (304.64 to 385.05)	127		314.97 (264.69 to 374.81)
(<45 years)	Yes	36	1177.4	305.76 (220.56 to 423.89)	25	ງ, ສາ96 <mark>60</mark>	418.92 (283.07 to 619.97)
DML $low(<19.5)$	No	289	8876.1	325.59 (290.14 to 365.38)	141	SH 3670	322.87 (273.75 to 380.82)
DIVII - 10W (<18.3)	Yes	11	187.0	588.16 (325.72 to 1062.04)	4		322.63 (121.09 to 859.62)
Dhoumataid Anthritic	No	289	8457.8	341.70 (304.49 to 383.45)	139		336.15 (284.66 to 396.94)
Kneumatoid Artiffitis	Yes	27	895.0	301.69 (206.90 to 439.93)	13	2025 010gie	263.29 (152.88 to 453.43)
			[Table c	continues on the next page]		at Agence Bibliogra s.	

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]	Derivation		8898 clud	alidation
Risk Factor cont.		No of incident cases	Total Person years	Crude Incidence Rate per 10000 person years (95% CI)	No of incident cases	area area area area area area area area	Crude Incidence Rate per 10000 person years (95% CI)
Secondaria Ostara anasia	No	262	7846.5	333.9 (295.83 to 376.89)	122	11,20 15,20 1,20 1,20	316.60 (265.12 to 378.07)
Secondary Osteoporosis	Yes	54	1506.2	358.51 (274.58 to 468.10)	30	18:1D	386.89 (270.51 to 553.34)
Duraniana Encatana	No	144	6832.0	210.77 (179.01 to 248.17)	63		189.79 (148.26 to 242.95)
Previous Fracture	Yes	172	2520.8	682.32 (587.61 to 792.31)	89	vi ann Ngari	679.69 (552.18 to 836.64)
	None	144	6832.0	210.77 (179.01 to 248.17)	63	d dat dat ()	189.79 (148.26 to 242.95)
Descriptions Free strong data it	1 fracture	105	1919.6	546.99 (451.76 to 662.29)	52	a Am Mir Mir	495.36 (377.47 to 650.07)
Previous Fracture, detail	2-4 fractures	57	557.9	1021.62 (788.04 to 1324.45)	33	ning,36 <mark>%</mark>	1397.28 (993.37 to 1965.44
	5+ fractures	10	43.2	2311.27 (1243.59 to 4295.60)	4	A tra	1701.81 (638.72 to 4534.31
Total		316	9352.8	337.87 (302.60 to 377.25)	152	36288	328.38 (280.11 to 384.96)

316 9352.8 337.87 (302.60 to 377.25) 152 G22.88 and similar technologies. and similar technologies. peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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Supplementary Figure 1 Predicted and Observed risk by 10th of predicted risk for each risk prediction model in the derivation dataset.



TRIPOD Checklist: Prediction Model Development and Validation

Section/ I Opic	item		Checklist item	Pag		
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the	1		
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size,	3		
ntroduction			predictors, outcome, statistical analysis, results, and conclusions.			
		1	Explain the medical context (including whether diagnostic or prognostic) and rationale			
Background	3a	D;V	for developing or validating the multivariable prediction model, including references to existing models.	5		
and objectives	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both	5		
Methods						
	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data) separately for the development and validation data sets if applicable	6		
Source of data	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up	6		
	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general	6		
Participants	5h	D·V	population) including number and location of centres.	6		
	50	D,V	Give details of treatments received, if relevant	-		
Outcomo	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed	6		
Outcome	6b	D·V	Report any actions to blind assessment of the outcome to be predicted	_		
	7-	D.)	Clearly define all predictors used in developing or validating the multivariable prediction	~		
Predictors	/a	D;V	model, including how and when they were measured.	6/		
	7h	D·V	Report any actions to blind assessment of predictors for the outcome and other	_		
Comple size		D.) (predictors.			
Sample size	8	D;V	Explain now the study size was arrived at.	-		
Missing data	9	D;V	imputation, multiple imputation) with details of any imputation method	7		
	10a	D	Describe how predictors were handled in the analyses.	6/		
	10h		Specify type of model, all model-building procedures (including any predictor selection),	-		
Statistical	dui	U	and method for internal validation.			
analysis	10c	V	For validation, describe how the predictions were calculated.	6/		
metnoas	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models	7/		
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation. if done.	7		
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	8		
Development	12	V	For validation, identify any differences from the development data in setting, eligibility	7		
vs. validation		L .	criteria, outcome, and predictors.	<u> </u>		
veaulia	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	g		
Participants	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	9		
	13c	V	For validation, show a comparison with the development data of the distribution of	10/		
	140		Important variables (demographics, predictors and outcome).			
Model	148	U	Specify the number of participants and outcome events in each analysis.	,		
development	14b	D	outcome.	1		
Model	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point)	Su de		
specification	15b	D	Explain how to the use the prediction model.	Su		
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	13/		
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance)	13/		
Discussion						
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	15/		
Internet 11	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	1		
interpretation	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	15/		
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	16		
Other information						
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Sup dc		
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.			

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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Does Bone Mineral Density Improve the Predictive Accuracy of Fracture Risk Assessment? A Prospective Cohort Study in Northern Denmark.

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Primary Subject Heading :	General practice / Family practice
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Keywords:	risk prediction, osteoporosis, fracture, predictive accuracy, bone mineral density



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2	Title
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Competing Interests

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

All authors have completed the ICMJE uniform disclosure form at <u>www.icmje.org/coi_disclosure.pdf</u> and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration

The lead author (Dr Dhiman) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical Approval

Ethics approval was given through the Region of North Jutland's from the Danish Data Protection Agency ("paraplyanmeldelse 2008-58-0028").

Funding

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NIHR acknowledgement

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Disclaimer

The views expressed are those of the author(s) and not necessarily those of the NIHR, the NHS or the Department of Health.

Patient Involvement

Patients were not involved in the development of this research question.

Data Sharing Statement

Data sharing: Technical appendix and statistical code is available from the corresponding author at paula.dhiman@nottingham.ac.uk. Due to restrictions by the Danish Data Protection Agency, data can only be shared on an aggregated level and by special permission.

Contributorship

Contributors: PD wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. PV and SA provided the AURORA dataset for analysis and linked patients to the National Patient Registry of Denmark, they also reviewed and revised the draft paper. NQ and TM provided clinical expertise, and reviewed and revised the draft paper.

Abstract:

Objective: To evaluate the added predictive accuracy of bone mineral density (BMD) to fracture risk assessment.

Design: Prospective cohort study using data between 01/01/2010 and 31/12/2012.

Setting: North Denmark Osteoporosis Clinic of referred patients presenting with at least one fracture risk factor to the referring doctor.

Participants: Patients aged 40-90 years; had BMD T-score recorded at the hip; and not taking osteoporotic preventing drugs for more than 1-year prior to baseline.

Main outcome measures: Incident diagnoses of osteoporotic fractures (hip, spine, forearm, humerus, and pelvis) were identified using the National Patient Registry of Denmark during 01/01/2012-01/01/2014. Cox regression was used to develop a fracture model based on predictors in the Fracture Risk Assessment Tool (FRAX®), with and without, binary and continuous BMD. Change in Harrell's C-Index and Reclassification tables were used to describe the added statistical value of BMD.

Results: Adjusting for predictors included in FRAX®, osteoporotic patients (T-score \leq -2.5) had 75% higher hazard of a fracture compared to patients with higher BMD (HR:1.75 (95% CI:1.28 to 2.38)). Forty-percent lower hazard was found per unit increase in continuous BMD T-score (HR:0.60 (95% CI:0.52 to 0.69)).

Accuracy improved marginally, and Harrell's C-Index increased by 1.2% when adding continuous BMD (0.76 to 0.77). Reclassification tables showed continuous BMD shifted 529 patients into different risk categories; 292 of these were reclassified correctly (57%; 95% CI:55% to 64%). Adding binary BMD however no improvement: Harrell's C-Index decreased by 0.6%.

Conclusions: Continuous bone mineral density marginally improves fracture risk assessment. Importantly, this was only found when using continuous BMD measurement for osteoporosis. It is suggested that future focus should be on evaluation of this risk factor using routinely collected data, and on the development of more clinically relevant methodology to assess the added value of a new risk factor

Article Summary

Strengths and Limitations:

- Addresses a research question recommended by The National Institute for Health and Care Excellence to investigate the added value of bone mineral density to fracture risk prediction.
- Investigates bone mineral density in both the commonly used, binary, and continuous • format.
- Presents changes in calibration, discrimination, and reclassification to describe the • added value of bone mineral density.
- Uses robustly collected data from Northern Denmark, with 3.2% missing data. •
- As data is from a North Danish population, with at least one fracture risk factor, this limits generalisability of the results. rainsaon...

Introduction

Osteoporosis causes over 8.9 million fractures worldwide, of which over 4.5 million occur in the USA and Europe, and account for 2.8 million disability adjusted life years (1). Further, 1.2 million disability adjusted life years are accounted for by hip fractures, which are projected to increase to 6 million by 2050 (2).

Given this burden, and treatment options for osteoporosis, identifying patients at risk of an osteoporotic fracture is high priority amongst health policymakers to reduce the risk of future fracture (3). Risk prediction tools have been developed to aid in the identification of patients at risk. For example, the Fracture Risk Assessment Tool (FRAX®) and QFracture® are commonly used to assess fracture risk in patients based on pre-defined risk factors.

Bone mineral density (BMD), a measurement used to aid diagnosis of osteoporosis, has also been identified as a fracture risk factor (4-7). Unlike some other fracture risk factors, treatment options (e.g. bisphosphonate medication) are available that reduces the fracture risk markedly when treatment is initiated based on low BMD.

English National guidelines (The National Institute for Health and Care Excellence (NICE)) for fracture risk assessment recommend treatment of osteoporosis to prevent fractures but have not included BMD as a mandatory risk factor for fracture risk prediction tools to incorporate (8). This is partly due to the lack of robust evidence and limited generalisability of current research, which has particularly focused on evaluating BMD in postmenopausal women evaluating the added value of BMD to existing fracture risk factors (5-7).

The National Institute of Clinical Health and Excellence also recognise this gap in the evidence and have recommended research to assess the added value of BMD as a risk factor in fracture risk assessment (9).

The aim of this study is to assess the value of BMD measurement in addition to the standard fracture risk factors used in the FRAX® risk model using a robustly collected prospective cohort.

Methods

This paper has been written in accordance to the TRIPOD checklist.

Patient Involvement

Patients were not involved in the development of this research question and were not involved in the design of this study.

Study Design and Data Source

A prospective cohort study was conducted using patients from the Aalborg University Hospital Record for Osteoporosis Risk Assessment (AURORA) dataset; patients were followed up using the National Patient Registry of Denmark.

The AURORA dataset consists of patients attending the Osteoporosis Clinic at Aalborg University Hospital after a referral from their primary care physician. A referral was offered to patients with at least one risk factor for osteoporosis (low BMI, previous fracture, parental hip fracture, smoking status, alcohol consumption, glucocorticoid use, rheumatoid arthritis, and secondary osteoporosis) or if they were aged 80 years and above. Further detail of the data collection has been described elsewhere (10). The Danish National Patient Registry which collects inpatient and outpatient data from all Danish hospitals, was linked to the AURORA dataset through unique patient identifiers

Ethics approval was given through the Region of North Jutland's from the Danish Data Protection Agency ("paraplyanmeldelse 2008-58-0028").

Cohort selection

Data collection for AURORA began 1st January 2010 and was collected for 3 years (up to 31st December 2012). Patients were included if they were aged 40-90 years; had a BMD T-score at the hip; and were not taking any osteoporotic preventing drugs or any bone sparing drugs for more than one year prior to baseline.

Primary Outcome

The primary outcome measure was an incident osteoporotic fracture during follow up (01/01/2012 to 01/01/2014); defined as a diagnosis of a fracture at the hip, spine, forearm, humerus, and pelvis. Fractures at these sites resulting from traffic, work, and sports related accidents were excluded from the study. Relevant fractures were identified in the Danish National Patient Registry, using the International Statistical Classification of Diseases, 10th Version codes (ICD-10 codes), which was developed using recognised database methodology for each fracture (11).

Fracture risk factors

Fracture risk factors, used in the FRAX® risk prediction model, were extracted at baseline. They were: age; gender; height (m); weight (kg); previous fracture; parental history of hip fracture, current smoking status; current alcohol consumption; glucocorticoid use (currently exposed for 3+ months); rheumatoid arthritis; and secondary osteoporosis (includes type I diabetes; osteogenesis imperfecta in adults; untreated, long standing hyperthyroidism;

hypogonadism; premature menopause (<45 years); chronic malnutrition; malabsorption; and chronic liver disease).

Bone Mineral Density

DXA scans were performed by trained technicians using Hologic Discovery A (Bedford, MA, USA). A daily QC programme was in place and in vivo CV using repositioning of patients was <1%. Total hip BMD was used as region of interest. Bone mineral density was added to the fracture risk prediction model twice, firstly, as a continuously measured T-score value, and secondly, as a binary risk factor, dichotomised at/above T-score threshold for osteoporosis and below threshold, -2.5 in T-score (manufacturers' normal range using normal material from T Kelly et al (12)) based on World Health Organisation (WHO) classifications (13). Calculated T-scores were gender specific.

Statistical Analysis

A complete case analysis was performed on the data; 3.2% of data was missing. The AURORA dataset was split into two using recognised methodology (14); where a random number was assigned to patients and based on a cut off, two-thirds was used to derive the risk models, and the remaining third was used to validate them.

Model derivation

Three Cox proportional hazards models were developed for the primary outcome, using a complete case analysis on the derivation dataset:

- Model 1. Standard fracture risk factors only (without BMD)
- Model 2. Standard fracture risk factors (with binary BMD)
- Model 3. Standard fracture risk factors (with continuous BMD)

Graphical methods were used (log-log plots) to assess the proportional hazards assumption, and risk factors violating this assumption were added to the model as a time varying covariate.

Recognised methodology used in research studies was used to build the 3 risk prediction models (15, 16); the Kaplan Meier method was used to obtain 4-year fracture risk estimates for patients. Further detail on the conversion of the Cox proportional hazards models to risk prediction models has been provided in Supplementary Table 1.

Validation of Models

Four-year fracture risk was calculated from each model and the predictive performance of each risk prediction model was assessed by measures describing calibration, discrimination, and reclassification. These metrics were assessed using the validation cohort.

Calibration measures how well the predicted risk agrees with observed risk in the data. It plots the mean predicted and observed risk of fracture for each decile of predicted risk. The observed risk of fracture was derived from the 4 year Kaplan-Meier estimate. Good calibration indicates the predicted risk is close to the observed risk of the outcome.

Discrimination measures how well the risk prediction model differentiates between patients who have or have not observed the event in the study. This was quantified by the area under

the receiver operating characteristic (ROC) curve (AUC), given by Harrell's C-Index with higher values indicating better discrimination.

Reclassification tables (17) measures movement between risk categories when adding a new risk factor. Threshold for treatment at 4 years was set at a fracture risk level of 8.5%; to be comparable to the treatment threshold of 20% at 10 years. This was presented by the total percent of patients reclassified (incorrectly and correctly), and also the Net Reclassification Index (NRI) (18, 19). The NRI gives the net calculation of the changes in the right direction and a higher NRI indicates a better reclassifying model.

All analyses were carried out using Stata (version 12) (20).

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Results

Characteristics of the data

The AURORA collected data on 7,912 patients; 1,795 patients were excluded comprising, 440 not aged between 40-90 years at baseline; 156 not having a recorded T-score value for the total hip at baseline; and 1,199 patients were taking anti-osteoporotic drug therapy for more than one year prior to baseline.

The study sample consisted of 6,117 patients; predominantly female (79.6%), and patients with a mean age of 62.9 (SD: 10.9) years. Two-thirds of this sample (n=4,093) was used for the derivation dataset and one-third (n=2,094) was used for the validation dataset. Table 1 presents the baseline characteristics of the study by derivation and validation dataset, and shows little difference between the datasets.

Patients in the derivation dataset had a median follow up time of 2.30 years [1.57, 2.99], and observed 318 (7.8%) osteoporotic fractures during follow up. Of these, 316 fractures were eligible for the analysis (2 patients had a fractures on or prior to baseline and were excluded). Patients contributed 9352.8 person years of observation, giving a total incidence rate of 337.87 per 10,000 person years (95% CI:302.60 to 377.25).

Fractures during follow up were predominantly found in the forearm (27.0%) and hip (17.9%). Higher fracture incidence rates were found in patients classed as osteoporotic, based on their T-score at both the total hip (809.73 per 10,000 person years (95% CI:641.68 to 1021.78)) and spine (L1-L4) (553.59 per 10,000 person years (95% CI:462.55 to 662.55)) (Supplementary Table 2).

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Table 1. Baseline characteristics of the derivation and	l validation datasets,	including missing
data.		

Characteristic			Derivation (n=4,093)		Validation (n=2,024)		
			No	%	No	%	
Gender	Female		3,266	79.8	1,602	79.2	
	Male		827	20.2	422	20.8	
Osteoporotic (Hip DXA)	No		3,683	90.0	1,820	89.9	
	Yes		410	10.0	204	10.1	
Osteoporotic Status (based on	Normal		1,886	46.1	927	45.8	
UK guidelines)	Osteopenic		1,797	43.9	893	44.1	
	Osteoporotic		410	10.0	204	10.1	
Previous Fracture	No		2,935	71.7	1,423	70.3	
	Yes		1,158	28.3	601	29.7	
No of Previous Fractures	None		2,935	71.7	1,423	70.3	
	1 fracture		862	21.1	467	23.1	
	2-4 fractures		270	6.6	122	6.0	
	5+ fractures		26	0.6	12	0.6	
Parental History of Hip Fracture	No		2,755	67.3	1,359	67.1	
	Yes		1,338	32.7	665	32.9	
Current Smoking Status	other (non/ex)		3,182	77.7	1,529	75.5	
-	smoker		911	22.3	495	24.5	
Alcohol Consumption	≤3 units per day		3,875	94.7	1,923	95.0	
	>3 units per day		218	5.3	101	5.0	
Glucocorticoid Use	No		3,577	87.4	1,741	86.0	
	Yes		516	12.6	283	14.0	
Rheumatoid Arthritis	No		3,686	90.1	1,801	88.0	
	Yes		407	9.9	223	11.0	
Other Bone Affecting Disease	No		2,382	58.2	1,139	56.3	
	Yes		1,711	41.8	885	43.7	
Secondary Osteoporosis	No		3,438	84.0	1,689	83.5	
	Yes		655	16.0	335	16.6	
	By disease						
	Type 1 diabetes	No	4,010	98.0	1,981	97.9	
		Yes	83	2.0	43	2.1	
	Osteogenesis	No	4,093	100	2,024	100	
		Yes	0	0	0	0	
	Hyperthyroidism	No	4,089	99.9	2,023	99.9	
		Yes	4	0.1	1	0.1	
	Malnutrition	No	4,090	99.9	2,023	99.9	
		Yes	3	0.1	1	0.1	
	Chronic Liver Disease	No	4,006	97.9	1,979	97.8	
		Yes	87	2.1	45	2.2	
	Menopause (Females only)**	No	853	26.1	405	25.3	
		Yes	2,413	73.9	1,197	74.7	

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	Premature Menopause (<45 years)***	No	1,904	78.9	941	78.6
		Yes	509	21.1	256	21.4
			Mean	SD	Mean	SD
Age (years)			62.9	10.9	63.0	11.0
Weight (kg)			72.1	15.5	72.2	15.9
	Missing		47	1.2	12	0.6
Height (m)			1.7	0.1	1.7	0.1
	Missing		131	3.2	61	3.0
BMI			26.4	5.0	26.4	5.1
	Missing		135	3.3	63	3.1
Hin DXA T-score			-11	11	-12	11

*out of patients with a fracture

**proportion out of respective number of females

***proportion out of respective number of females with menopause

Model development

The unadjusted analysis showed statistically significant association between BMD (continuous and binary) and osteoporotic fracture (HR=0.55; 95% CI: 0.50 to 0.61, p<0.001, HR=2.79; 95% CI: 2.11 to 3.67, p<0.001, respectively). Significant associations with fracture were also found with age (HR=1.03; 95% CI: 1.02 to 1.04, p<0.001), previous fracture (HR=3.38; 95% CI: 2.69 to 4.24, p<0.001), BMI (HR=0.97; 95% CI: 0.95 to 1.00, p=0.03), and gender (HR=0.73; 95% CI: 0.53 to 1.00, p=0.05). Further, a time-varying effect was found in patients with a previous fracture; hazard of a subsequent fracture was highest in the first year during follow up and decreased per year of follow up (p<0.001).

The adjusted analysis is presented in Table 2. Model 1 showed that of the standard risk factors, age and previous fracture were significantly associated with fracture; hazard of fracture increased by 2% per year increase in age (HR=1.02; 95% CI: 1.01 to 1.04); and increased almost 5 fold in patients with a previous fracture at time 0 years (HR=4.88; 95% CI: 3.37 to 7.08).

Hazard of fracture increased by 75% for patients classed as osteoporotic by their BMD score (Model 2, HR=1.75; 95% CI: 1.28 to 2.38). Hazard of fracture also decreased by 40% per SD improvement in BMD T-score (Model 3, HR=0.60; 95% CI: 0.52 to 0.69).

		Adjı	usted Hazard Ratio (959	% CI)
Risk Factor		Model 1: Standard Risk Factors only	Model 2: Standard Risk Factors + BMD (categorical)	Model 3: Standard Risk Factors + BMD (continuous)
Age (years)		1.024 (1.013 to 1.036)	1.019 (1.007 to 1.031)	1.007 (0.995 to 1.019)
Gender	Female	Ref	Ref	Ref
Gender	Male	0.754 (0.544 to 1.044)	0.796 (0.573 to 1.104)	0.851 (0.613 to 1.181)
BMI		0.978 (0.954 to 1.002)	0.989 (0.965 to 1.013)	1.027 (1.000 to 1.055)
Provious Fracture	No	Ref	Ref	Ref
Flevious Flacture	Yes (time = 0 years)	4.88 (3.336 to 7.078)	4.667 (3.214 to 6.778)	4.018 (2.763 to 5.842)
Demonstral History of His Erecture	No	Ref	Ref	Ref
Parental History of Hip Fracture	Yes	1.079 (0.834 to 1.397)	1.096 (0.847 to 1.419)	1.105 (0.854 to 1.430)
Convert Surveiller	No	Ref	Ref	Ref
Current Smoker	Yes	1.121 (0.852 to 1.475)	1.076 (0.817 to 1.417)	1.019 (0.774 to 1.342)
	No	Ref	Ref	Ref
Alcohol Consumption (>3 units/day)	Yes	1.414 (0.904 to 2.212)	1.440 (0.921 to 2.252)	1.459 (0.932 to 2.283)
Characteristic	No	Ref	Ref	Ref
Glucocorticola Use	Yes	1.080 (0.753 to 1.550)	1.052 (0.733 to 1.510)	1.038 (0.724 to 1.489)
DL	No	Ref	Ref	Ref
Rneumatoid Arthritis	Yes	1.098 (0.731 to 1.650)	1.089 (0.725 to 1.637)	1.116 (0.742 to 1.678)
	No	Ref	Ref	Ref
Secondary Osteoporosis	Yes	0.993 (0.729 to 1.354)	0.966 (0.708 to 1.317)	0.911 (0.667 to 1.243)
Osteoporotic	No	Ref	Ref	Ref
	Yes	-	1.745 (1.279 to 2.381)	-
Hip DXA T-score (SD)		-	-	0.600 (0.524 to 0.686)
Previous Fracture (TVC [*])		0.635 (0.489 to 0.826)	0.639 (0.492 to 0.830)	0.644 (0.495 to 0.837)

Table 2. Multivariable analysis for osteoporotic fracture in the derivation cohort. Data are adjusted hazard ratios and 95% confidence intervals.

*TVC = time varying covariate, value is interaction effect and 95% CI.

Model Validation

The 4-year predicted risk of fracture was calculated for all patients in the validation dataset; this was compared to the observed fracture outcome within the 4 year follow up.

Calibration and Discrimination

Calibration plots suggested some improvement when adding BMD measurement; particularly when including continuous BMD T-score measurement (Model 3; Supplementary Figure 1).

The largest change in discrimination was found when adding continuous BMD measurement to standard risk factors; Harrell's C-Index increased by 1.17% (Table 3). However, binary BMD measurement, as a measure for osteoporotic patients, was found to reduce Harrell's C-Index by -0.65%.

Table 3. Harrell's C-Index for Model 1, 2, 3, 4, and 5.

	(% change)*
0.764 (0.718 to 0.810)	-
0.759 (0.712 to 0.806)	-0.005 (-0.65%)
0.773 (0.732 to 0.814)	0.009 (1.17%)
	0.764 (0.718 to 0.810) 0.759 (0.712 to 0.806) 0.773 (0.732 to 0.814)

Reclassification

Reclassification tables indicated that adding continuous BMD measurement improved classification of patients into their correct risk categories. This was not found when adding binary BMD. Table 4 presents the reclassification table for Model 1 (standard fracture risk factors only) and Model 3 (standard risk factors with continuous BMD), using the 8.5% prespecified risk threshold.
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			Model 3: continuo	SRF with us BMD			
			<8.5%	≥8.5%	Total	Total No.(%) Reclassified	
		No	391	227			
M 114		%	63.3%	36.7%			
Model 1: SRF	<8.5%	No. Events	5	9	618	227 (36.7%)	
without BMD		No. Non events	386	218			
	C	Observed Event Rate	served Event Rate 1.3% 4.0%				
		No	302	1,040			
		%	22.5%	77.5%			
	≥8.5%	No. Events	10	121	1,342	302 (22.5%)	
		No. Non events	292	919			
		Observed Event Rate	3.3%	11.6%			
	Total		693	1,267	1,960	529 (27.0%)	

Table 4. Risk Reclassification Table comparing Model 1 (standard fracture risk factors alone)to Model 3 (standard fracture risk factors with continuous BMD measurement), using a clinical8.5% risk cut off.

Of the 1,960 patients in the validation dataset, 27% (n=529) were reclassified into a different risk category when including continuous BMD into fracture risk prediction. Two percent (9/529) were found to be reclassified correctly into a higher risk group and 55% (292/529) were reclassified correctly into a lower risk group; indicating 22% (292/1342) of patients at high risk in Model 1, not accounting for BMD measurement, were no longer at high risk. The net reclassification improvement when adding continuous BMD to standard risk factors, was 0.03, which resulted from increased specificity (non-event NRI = 4%) and decreased sensitivity (event NRI: -1%) from Model 1 (Table 5).

Table 5. Summary of Net Reclassification Index (NRI) and Integrated Discrimination Index (IDI) for all comparisons between developed fracture risk prediction models.

Comparison	Event NRI	Non-Event NRI	Overall NRI
Model 1 vs. Model 2	-3.45%	2.09%	-0.01
Model 1 vs. Model 3	-0.69%	4.08%	0.03

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Discussion

Summary of Findings

Bone mineral density showed significant association with fracture risk with a 40% decrease for each SD rise in BMD. However, this resulted in small improvements in calibration, discrimination, and reclassification. The c-index estimate was slightly higher with continuous BMD but this increase is not conclusive given the width of the confidence intervals. Despite the limited improvement found of 1% in discrimination when adding continuous BMD, reclassification tables showed 57% of reclassified patients moving into their correct risk group through improved specificity. Importantly, no improvement was found when adding BMD in a binary format.

Our findings are consistent with and corroborate with current literature (7, 21, 22). Specifically, a study conducted in the Netherlands with 4 year follow up, investigating the added value of BMD for hip fractures risk, found modest improvement in predictability (21). Further, two more recent studies also indicated limited added value of BMD to fracture risk prediction (7, 22).

Strengths and Limitations

Answering Evidence gap

To our knowledge, this is the first study to investigate the added value of BMD in a binary and continuous format, to standard fracture risk factors. Further, it is based on a larger sample size than other studies investigating BMD in addition to FRAX (7, 21, 22). It helps inform the NICE research recommendation to assess the added value of BMD to routine fracture risk assessment in primary care (23). It further highlights that the more commonly used for treatment decision making, binary format of BMD resulted in a loss of predictability in fracture risk prediction; based on comparable measures for discrimination and reclassification

Robustness of Data

The prospective cohort was well populated with key standard risk factors recorded: BMI, smoking status and alcohol consumption, and personal and parental fracture history. Other than 3.2% of missing data for BMI, in 6,117 patients, complete data was collected for all risk factors (including BMD T-score recorded at the total hip). Further, the cohort was linked to a national robust electronic health records. This Danish National Patient Registry allowed for outcome fracture to be identified and also provided data on the mechanism for the fracture; this helped more accurately phenotype osteoporotic fractures.

Generalisability

The generalisability is affected in a few ways. Firstly, the findings are based on a Danish cohort. Secondly, AURORA data was collected from patients who presented to their doctor with at least one fracture risk factor and were referred to the osteoporosis clinic; this led to a biased study sample with a higher risk of a fracture and increased age. This could overestimate fracture risk amongst patients in a primary care setting.

Methodology

Due to the increased age of the sample, death becomes a competing risk. However, information on death was not collected and could not be retrieved. This limited the analysis of the data as competing risks could not be accounted for which may again lead to an overestimation of fracture risk (24). However, as an independent study primarily assessing the added value of BMD through deriving and validating the fracture risk prediction models, this bias would be present in both analyses to compare derived risk models with and without BMD measurement.

The FRAX risk algorithm has not yet been published, therefore FRAX estimates could not be directly calculated for the cohort. Instead, the FRAX risk model was recalibrated on the dataset with and without BMD added. Further, fracture outcomes in this study included pelvic fractures which are increasingly recognised as low trauma fragility fractures [(25)], and used BMD taken at the total hip instead of at the femur neck as it is the gold standard in Denmark (26).

Internal validation was performed to validate the derived risk prediction models. This may lead to over optimistic results of the performance of the risk models (14). To account for this limitation, a commonly practised method which randomly assigns patients to the derivation and validation datasets was used; further, a similar 1:2 ratio was also used to split the data (27-29).

The study had a 4 year follow up which is shorter than other recognised risk models. To account for this, we adapted the 20% clinical risk threshold for 10 year fracture estimates to 8.5% for 4 year fracture estimates, assuming that risk is constant over time (30, 31).

Traditional methodology assessing the added value to risk factors to existing risk prediction models are criticised to be insensitive to change, to lack interpretability (32-35). This was shown when finding a 1% change in Harrell's C-Index and overlapping confidence intervals between models, limiting the interpretability of results. Reclassification analysis was thus also used to provide more clinically interpretable results.

Clinical implications

The most notable clinical implication is the more routine use of BMD measurement for fracture risk assessment. Further, evidence suggests continuous BMD adds better predictability compared to the binary format.

Future Research

Further research is recommended to evaluate the added value of BMD to fracture risk prediction; in particular in addition to QFracture risk factors and using primary care routinely collected data. However, a brief interrogation into the Clinical Practice Research Datalink, a routinely collected UK primary care database, showed poor availability of BMD measurement in patient records, and thus, strong limitations to potential analyses. Less than 1% of patients had BMD recorded from a sample of 60,658 patients aged 40-90; not on any osteoporotic treatment; and with complete data for age, gender, BMI, smoking status, and alcohol consumption. Thus, prior to UK analysis, BMD recording in primary care databases needs to improve.

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Methodologically, as well as assessing the added value of BMD to standard risk factors, we should also explore the option to replace existing fracture risk factors with the BMD measurement; this has rarely been explored in the literature but should be considered in future analyses. We also recommend research to investigate the added value of BMD in a potentially more natural, 3 group format of BMD (osteopenic, normal, osteoporotic).

In addition, further research is recommended to develop current methodology used to assess the added value of BMD to provide more clinically relevant results, such as cost implications; and to allow for better comparability between new risk factors with respect to their added value, thus improving decision making.

Conclusion

Continuous BMD marginally improves fracture risk assessment. Importantly, this was only found when using continuous BMD measurement for osteoporosis. It seems that prediction models for fragility fracture risk may be improved only marginally, using present risk factor assessment and evaluations. It is suggested that future focus should be on additional risk factors and on the development of more clinically relevant methodology to assess the added value of a new risk factor.

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Beta coefficients from each Cox regression model were used to create each fracture risk prediction model.

Once all 5 models were finalised, their beta coefficients were used to create 5 risk prediction models and calculate risk of fracture for each patient, using the following general equation:

$$\widehat{risk} = 1 - S_0(t)^{exp(\sum_{i=1}^p \beta_i X_i - \sum_{i=1}^p \beta_i \overline{X}_i)}$$

Where $S_0(t)$ is the baseline survival rate at follow up time, t(for this example, a follow up time of 10 years will be used); beta (β_i) are the regression coefficients for each included risk factor in the model (i); X_i is the observed data value for each risk factor; \overline{X}_i is the corresponding mean for each risk factor; and \mathbf{p} is the total number of risk factors included in the model. Table A1 shows the formula for each risk prediction model explicitly.

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$0.1138883* \text{mean smoking status} + 0.0773898* \text{mean glucocorticoid use} + 0.3465287* \text{mean alcohol consumption} + 0.0936966* \text{mean rheumatoid arthritis} - 0.0069432* \text{mean secondary osteoporosis} + -0.4535108* \text{mean (previous fracture} where \sum_{i=1}^{p} \beta_i X_i = 0.0186827* \text{age} + -0.228784* \text{gender} + -0.0113651* \text{BMI} + 1.540559* \text{previous fracture} + 0.092011* \text{parental hip fracture} + 0.0732564* \text{smoking status} + 0.0508706* \text{gluco} + 0.3649544* \text{alcohol consumption} + 0.0854353* \text{rheumatoid arthritis} + -0.034688 \text{osteoporosis} + 0.5568944* \text{osteoporosis} + -0.4481145* (\text{previous fracture}* \text{time}) where \sum_{i=1}^{p} \beta_i \overline{X}_i = 0.0186827* \text{mean age} + -0.228784* \text{mean gender} + -0.0113651* \text{mean BMI} + 1.540559* \text{mean previous fracture} + 0.0732564* \text{mean age} + -0.228784* \text{mean gender} + -0.0113651* \text{mean BMI} + 1.540559* \text{mean smoking status} + 0.0508706* \text{mean glucocorticoid use} + 0.0732564* \text{mean smoking status} + 0.0508706* \text{mean glucocorticoid use} + 0.3649544* \text{mean alcohol consumption} + 0.0854353* \text{mean rheumatoid arthritis} - 0.0346885* \text{mean secondary osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.0854353* \text{mean rheumatoid arthritis} - 0.0346885* \text{mean secondary osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.0508706* \text{mean rheumatoid arthritis} - 0.0346885* \text{mean secondary osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.0508706* \text{mean rheumatoid arthritis} - 0.0346885* \text{mean secondary osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.0508706* \text{mean osteoporosis} + 0.0346885* \text{mean secondary osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.0508706* \text{mean osteoporosis} + 0.0346885* \text{mean secondary osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.0346885* \text{mean secondary osteoporosis} + 0.5568944* \text{mean osteoporosis} + 0.0508706* \text{mean osteoporosis} + 0.0508706* \text{mean osteoporosis} + 0.0508706* \text{mean osteoporosis} + 0.0508$		1.585278*mean previous fracture+0.0762559*mean parental hip fracture+					
$0.3465287*\text{mean alcohol consumption}+0.0936966*\text{mean rheumatoid arthritis} -0.0069432*\text{mean secondary osteoporosis}+-0.4535108*\text{mean (previous fracture)} where \sum_{i=1}^{p} \beta_i X_i =0.0186827*age+-0.228784*gender+-0.0113651*BMI+1.540559*previous fracture + 0.092011*parental hip fracture+0.0732564*smoking status+0.0508706*glucore + 0.3649544*alcohol consumption+0.0854353*rheumatoid arthritis+-0.034688 + 0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+ 1.540559*mean previous fracture+0.092011*mean parental hip fracture+ 0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+ 0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis+ -0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+0.5568944*mean osteoporosis+ 0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+0.5568944*mea$		0.1138883*mean smoking status+0.0773898*mean glucocorticoid use+					
$-0.0069432*\text{mean secondary osteoporosis}+-0.4535108*\text{mean (previous fracture)}$ where $\sum_{i=1}^{p} \beta_i X_i =$ 0.0186827*age+-0.228784*gender+-0.0113651*BMI+1.540559*previous fracture) Model 2 0.092011*parental hip fracture+0.0732564*smoking status+0.0508706*glucoe 0.3649544*alcohol consumption+0.0854353*rheumatoid arthritis+ -0.034688 osteoporosis+0.5568944*osteoporosis+-0.4481145*(previous fracture*time) where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ 0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+ 1.540559*mean previous fracture+0.092011*mean parental hip fracture+ 0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+ 0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+		0.3465287*mean alcohol consumption+0.0936966*mean rheumatoid arthritis+					
where $\sum_{i=1}^{p} \beta_i X_i =$ 0.0186827*age+-0.228784*gender+-0.0113651*BMI+1.540559*previous fractional fracture in the interval of the int		-0.0069432*mean secondary osteoporosis+-0.4535108*mean (previous fracture					
Model 2 $0.0186827*age+-0.228784*gender+-0.0113651*BMI+1.540559*previous fractionModel 20.092011*parental hip fracture+0.0732564*smoking status+0.0508706*glucos0.3649544*alcohol consumption+0.0854353*rheumatoid arthritis+ -0.034688osteoporosis+0.5568944*osteoporosis+-0.4481145*(previous fracture*time)where \sum_{i=1}^{p} \beta_i \overline{X}_i =0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+1.540559*mean previous fracture+0.092011*mean parental hip fracture+0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+$		where $\sum_{i=1}^{p} \beta_i X_i =$					
Model 2 $0.092011*$ parental hip fracture+ $0.0732564*$ smoking status+ $0.0508706*$ gluco $0.3649544*$ alcohol consumption+ $0.0854353*$ rheumatoid arthritis+ - 0.034688 osteoporosis+ $0.5568944*$ osteoporosis+- $0.4481145*$ (previous fracture*time) where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ $0.0186827*$ mean age+- $0.228784*$ mean gender+- $0.0113651*$ mean BMI+ $1.540559*$ mean previous fracture+ $0.092011*$ mean parental hip fracture+ $0.0732564*$ mean smoking status+ $0.0508706*$ mean glucocorticoid use+ $0.3649544*$ mean alcohol consumption+ $0.0854353*$ mean rheumatoid arthritis- - $0.0346885*$ mean secondary osteoporosis+ $0.5568944*$ mean osteoporosis+		0.0186827*age+-0.228784*gender+-0.0113651*BMI+1.540559*previous fracto					
0.3649544*alcohol consumption+0.0854353*rheumatoid arthritis+ -0.034688 osteoporosis+0.5568944*osteoporosis+-0.4481145*(previous fracture*time) where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ 0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+ 1.540559*mean previous fracture+0.092011*mean parental hip fracture+ 0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+ 0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis- -0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+	Model 2	0.092011*parental hip fracture+0.0732564*smoking status+0.0508706*glucocorticoid					
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where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ 0.0186827*mean age+-0.228784*mean gender+-0.0113651*mean BMI+ 1.540559*mean previous fracture+0.092011*mean parental hip fracture+ 0.0732564*mean smoking status+0.0508706*mean glucocorticoid use+ 0.3649544*mean alcohol consumption+0.0854353*mean rheumatoid arthritis- -0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+		osteoporosis+0.5568944*osteoporosis+-0.4481145*(previous fracture*time)					
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		-0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+					
-0.4481145*mean (previous fracture*time)		-0.4481145*mean (previous fracture*time)					

cont.	Equation
cont	
	where $\sum_{i=1}^{i} \beta_i X_i =$
	0.0071931*age+-0.1615582*gender+0.0268478*BMI+1.39069*previous fracture+
	0.1000272*parental hip fracture+0.0192416*smoking status+0.0374944*glucocorticoid use
	0.3774416*alcohol consumption+0.1097646*rheumatoid arthritis+ -0.0932063*secondary
	osteoporosis+-0.5110986*t-score+-0.4404955*(previous fracture*time)
Model 3	where $\sum_{i=1}^{P} \beta_i X_i =$
	0.0071931*mean age+-0.1615582*mean gender+0.0268478*mean BMI+
	1.39069*mean previous fracture+0.1000272*mean parental hip fracture+
	0.0192416*mean smoking status+0.0374944*mean glucocorticoid use+
	0.3774416*mean alcohol consumption+0.1097646*mean rheumatoid arthritis+
	-0.0932063*mean secondary osteoporosis+-0.5110986*mean t-score+
	-0.4404955*mean (previous fracture*time)

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	No of incident	Total	Crude Incidence Rate per	No of	Tot	Curde Incidence Dote
	cases	No of incidentTotal PersonCrude Incidence Rate per 10000 person years (95% 				10000 person years (9 CI)
40-49	17	1169.9	145.31 (90.33 to 233.74)	12	lated	215.15 (122.19 to 378.
50-59	70	2534.7	276.17 (218.49 to 349.07)	33	to te	251.71 (178.95 to 354.
60-69	93	3062.9	303.63 (247.79 to 372.06)	42	uperi xtan	288.87 (213.48 to 390.
70-79	83	1906.0	435.46 (351.17 to 539.98)	49	d dan d dan	511.11 (386.29 to 676.
80-89	52	652.7	796.75 (607.13 to 1045.59)	16		460.56 (282.15 to 751)
90-99	1	26.6	376.51 (53.04 to 2672.85)	-	ning,	-
No	245	8475.9	289.05 (255.03 to 327.61)	123	<u>A</u> 16 <mark>39</mark> 1	295.31 (247.48 to 352.
Yes	71	876.8	809.73 (641.68 to 1021.78)	29		625.28 (434.52 to 899)
No	191	7025.8	271.86 (235.91 to 313.28)	111	g a 47 5 6	319.37 (265.16 to 384
Yes	119	2149.6	553.59 (462.55 to 662.55)	39		358.08 (261.63 to 490.
Female	266	7417.5	358.61 (318.01 to 404.40)	129		350.56 (295.00 to 416.
Male	50	1935.3	258.36 (195.82 to 340.88)	23	echno	242.36 (161.05 to 364.
No	220	6281.5	350.24 (306.88 to 399.71)	118	2010827	379.58 (316.92 to 454.
Yes	96	3071.3	312.57 (255.90 to 381.79)	34	.1520-2	223.66 (159.81 to 313
	40-49 50-59 60-69 70-79 80-89 90-99 No Yes No Yes Female Male No Yes	40-49 17 50-59 70 60-69 93 70-79 83 80-89 52 90-99 1 No 245 Yes 71 No 191 Yes 119 Female 266 Male 50 No 220 Yes 96	40-49171109.950-59702534.760-69933062.970-79831906.080-8952652.790-99126.6No2458475.9Yes71876.8No1917025.8Yes1192149.6Female2667417.5Male501935.3No2206281.5Yes963071.3	40-49171105.9143.31 (90.33 to 233.74)50-59702534.7276.17 (218.49 to 349.07)60-69933062.9303.63 (247.79 to 372.06)70-79831906.0435.46 (351.17 to 539.98)80-8952652.7796.75 (607.13 to 1045.59)90-99126.6376.51 (53.04 to 2672.85)No2458475.9289.05 (255.03 to 327.61)Yes71876.8809.73 (641.68 to 1021.78)No1917025.8271.86 (235.91 to 313.28)Yes1192149.6553.59 (462.55 to 662.55)Female2667417.5358.61 (318.01 to 404.40)Male501935.3258.36 (195.82 to 340.88)No2206281.5350.24 (306.88 to 399.71)Yes963071.3312.57 (255.90 to 381.79)	40-49171105.9143.31 (90.33 to 233.74)1250-59702534.7276.17 (218.49 to 349.07)3360-69933062.9303.63 (247.79 to 372.06)4270-79831906.0435.46 (351.17 to 539.98)4980-8952652.7796.75 (607.13 to 1045.59)1690-99126.6376.51 (53.04 to 2672.85)-No2458475.9289.05 (255.03 to 327.61)123Yes71876.8809.73 (641.68 to 1021.78)29No1917025.8271.86 (235.91 to 313.28)111Yes1192149.6553.59 (462.55 to 662.55)39Female2667417.5358.61 (318.01 to 404.40)129Male501935.3258.36 (195.82 to 340.88)23No2206281.5350.24 (306.88 to 399.71)118Yes963071.3312.57 (255.90 to 381.79)34	40-49171109.9143.31 (90.33 to 233.74)12aray to50-59702534.7276.17 (218.49 to 349.07)3360-69933062.9303.63 (247.79 to 372.06)4270-79831906.0435.46 (351.17 to 539.98)4980-8952652.7796.75 (607.13 to 1045.59)1690-99126.6376.51 (53.04 to 2672.85)-No2458475.9289.05 (255.03 to 327.61)123Yes71876.8809.73 (641.68 to 1021.78)29No1917025.8271.86 (235.91 to 313.28)111Yes1192149.6553.59 (462.55 to 662.55)39Female2667417.5358.61 (318.01 to 404.40)129Male501935.3258.36 (195.82 to 340.88)23No2206281.5350.24 (306.88 to 399.71)11891067Yes963071.3312.57 (255.90 to 381.79)34152.92

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		Derivation			alidation		
Risk Factor cont.		No of incident cases	Total Person years	Crude Incidence Rate per 10000 person years (95% CI)	No of incident cases	area and a construction of the construction of	Crude Incidence Rate per 10000 person years (95% CI)
Current Smoker	No	240	7279.1	329.71 (290.53 to 374.18)	103		293.19 (241.70 to 355.65)
Current Smoker	Yes	76	2073.7	366.5 (292.71 to 458.90)	49		439.16 (331.91 to 581.07)
Alcohol Consumption	No	293	8875.9	330.11 (294.39 to 370.15)	140	to te S	318.2 (269.63 to 375.53)
more than 3 units per day	Yes	23	476.9	482.33 (320.52 to 725.83)	12	oade uperi xt'anc	523.66 (297.39 to 922.09)
Glucocorticoid Use (3	No	279	8184.5	340.89 (303.15 to 383.33)	132		330.57 (278.73 to 392.06)
months)	Yes	37	1168.3	316.7 (229.47 to 437.11)	20	a min	314.57 (202.95 to 487.59)
Menopause	No	68	1962.8	346.44 (273.15 to 439.39)	29	<u>بو</u> 28	312.19 (216.94 to 449.24)
	Yes	198	5454.7	362.99 (315.79 to 417.24)	100	A Hrs	363.52 (298.82 to 442.23)
Premature Menopause (<45 years)	No	280	8175.4	342.49 (304.64 to 385.05)	127		314.97 (264.69 to 374.81)
	Yes	36	1177.4	305.76 (220.56 to 423.89)	25	ງ, ສາ96 <mark>60</mark>	418.92 (283.07 to 619.97)
DML $low(<19.5)$	No	289	8876.1	325.59 (290.14 to 365.38)	141	SH 3670	322.87 (273.75 to 380.82)
ыли - юw (<18.5)	Yes	11	187.0	588.16 (325.72 to 1062.04)	4		322.63 (121.09 to 859.62)
Dhoumataid Anthritic	No	289	8457.8	341.70 (304.49 to 383.45)	139		336.15 (284.66 to 396.94)
Kneumatoid Artiffitis	Yes	27	895.0	301.69 (206.90 to 439.93)	13	2025 010gie	263.29 (152.88 to 453.43)
			[Table c	continues on the next page]		at Agence Bibliogra s.	

Page 25 of 27

]	Derivation		8898 clud	alidation
Risk Factor cont.		No of incident cases	Total Person years	Crude Incidence Rate per 10000 person years (95% CI)	No of incident cases	area area area area area area area area	Crude Incidence Rate per 10000 person years (95% CI)
Secondaria Ostara anasia	No	262	7846.5	333.9 (295.83 to 376.89)	122	11,20 15,20 12,20	316.60 (265.12 to 378.07)
Secondary Osteoporosis	Yes	54	1506.2	358.51 (274.58 to 468.10)	30	18:1D	386.89 (270.51 to 553.34)
Previous Fracture	No	144	6832.0	210.77 (179.01 to 248.17)	63		189.79 (148.26 to 242.95)
	Yes	172	2520.8	682.32 (587.61 to 792.31)	89	vi ann Ngari	679.69 (552.18 to 836.64)
Previous Fracture, detail	None	144	6832.0	210.77 (179.01 to 248.17)	63	d dat dat ()	189.79 (148.26 to 242.95)
	1 fracture	105	1919.6	546.99 (451.76 to 662.29)	52	a Am Mir Mir	495.36 (377.47 to 650.07)
	2-4 fractures	57	557.9	1021.62 (788.04 to 1324.45)	33	ning,36 <mark>%</mark>	1397.28 (993.37 to 1965.44
	5+ fractures	10	43.2	2311.27 (1243.59 to 4295.60)	4	A tra	1701.81 (638.72 to 4534.31
Total		316	9352.8	337.87 (302.60 to 377.25)	152	36288	328.38 (280.11 to 384.96)

316 9352.8 337.87 (302.60 to 377.25) 152 G22.88 and similar technologies. and similar technologies. peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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Supplementary Figure 1 Predicted and Observed risk by 10th of predicted risk for each risk prediction model in the derivation dataset.



TRIPOD Checklist: Prediction Model Development and Validation

Section/ I Opic	item		Checklist item	Pag
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size,	3
ntroduction			predictors, outcome, statistical analysis, results, and conclusions.	
		1	Explain the medical context (including whether diagnostic or prognostic) and rationale	
Background	3a	D;V	for developing or validating the multivariable prediction model, including references to existing models.	5
and objectives	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both	5
Methods				
	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data) separately for the development and validation data sets if applicable	6
Source of data	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up	6
	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general	6
Participants	5h	D·V	population) including number and location of centres.	6
	50	D,V	Give details of treatments received, if relevant	-
Outcomo	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed	6
Outcome	6b	D·V	Report any actions to blind assessment of the outcome to be predicted	_
	7-	D.) (Clearly define all predictors used in developing or validating the multivariable prediction	~
Predictors	/a	D;V	model, including how and when they were measured.	6/
	7h	D·V	Report any actions to blind assessment of predictors for the outcome and other	_
Comple size		D.) (predictors.	
Sample size	8	D;V	Explain now the study size was arrived at.	-
Missing data	9	D;V	imputation, multiple imputation) with details of any imputation method	7
	10a	D	Describe how predictors were handled in the analyses.	6/
	10h		Specify type of model, all model-building procedures (including any predictor selection),	-
Statistical	dui	U	and method for internal validation.	
analysis	10c	V	For validation, describe how the predictions were calculated.	6/
metnoas	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models	7/
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation. if done.	7
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	8
Development	12	V	For validation, identify any differences from the development data in setting, eligibility	7
vs. validation		L .	criteria, outcome, and predictors.	<u> </u>
veaulia	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	g
Participants	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	9
	13c	V	For validation, show a comparison with the development data of the distribution of	10/
	140		Important variables (demographics, predictors and outcome).	
Model	148	U	Specify the number of participants and outcome events in each analysis.	,
development	14b	D	outcome.	1
Model	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point)	Su de
specification	15b	D	Explain how to the use the prediction model.	Su
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	13/
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance)	13/
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	15/
Internet 11	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	1
interpretation	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	15/
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	16
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Sup dc
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	2

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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Does Bone Mineral Density Improve the Predictive Accuracy of Fracture Risk Assessment? A Prospective Cohort Study in Northern Denmark.

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2	Title
3 4	The
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Competing Interests

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

All authors have completed the ICMJE uniform disclosure form at <u>www.icmje.org/coi_disclosure.pdf</u> and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration

The lead author (Dr Dhiman) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical Approval

Ethics approval was given through the Region of North Jutland's from the Danish Data Protection Agency ("paraplyanmeldelse 2008-58-0028").

Funding

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Disclaimer

The views expressed are those of the author(s) and not necessarily those of the NIHR, the NHS or the Department of Health.

Patient Involvement

Patients were not involved in the development of this research question.

Data Sharing Statement

Data sharing: Technical appendix and statistical code is available from the corresponding author at paula.dhiman@nottingham.ac.uk. Due to restrictions by the Danish Data Protection Agency, data can only be shared on an aggregated level and by special permission.

Contributorship

Contributors: PD wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. PV and SA provided the AURORA dataset for analysis and linked patients to the National Patient Registry of Denmark, they also reviewed and revised

the draft paper. NQ and TM provided clinical expertise, and reviewed and revised the draft paper.

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Abstract:

Objective: To evaluate the added predictive accuracy of bone mineral density (BMD) to fracture risk assessment.

Design: Prospective cohort study using data between 01/01/2010 and 31/12/2012.

Setting: North Denmark Osteoporosis Clinic of referred patients presenting with at least one fracture risk factor to the referring doctor.

Participants: Patients aged 40-90 years; had BMD T-score recorded at the hip; and not taking osteoporotic preventing drugs for more than 1-year prior to baseline.

Main outcome measures: Incident diagnoses of osteoporotic fractures (hip, spine, forearm, humerus, and pelvis) were identified using the National Patient Registry of Denmark during 01/01/2012-01/01/2014. Cox regression was used to develop a fracture model based on predictors in the Fracture Risk Assessment Tool (FRAX®), with and without, binary and continuous BMD. Change in Harrell's C-Index and Reclassification tables were used to describe the added statistical value of BMD.

Results: Adjusting for predictors included in FRAX®, osteoporotic patients (T-score \leq -2.5) had 75% higher hazard of a fracture compared to patients with higher BMD (HR:1.75 (95% CI:1.28 to 2.38)). Forty-percent lower hazard was found per unit increase in continuous BMD T-score (HR:0.60 (95% CI:0.52 to 0.69)).

Accuracy improved marginally, and Harrell's C-Index increased by 1.2% when adding continuous BMD (0.76 to 0.77). Reclassification tables showed continuous BMD shifted 529 patients into different risk categories; 292 of these were reclassified correctly (57%; 95% CI:55% to 64%). Adding binary BMD however no improvement: Harrell's C-Index decreased by 0.6%.

Conclusions: Continuous bone mineral density marginally improves fracture risk assessment. Importantly, this was only found when using continuous BMD measurement for osteoporosis. It is suggested that future focus should be on evaluation of this risk factor using routinely collected data, and on the development of more clinically relevant methodology to assess the added value of a new risk factor

Article Summary

Strengths and Limitations:

- Addresses a research question recommended by The National Institute for Health and Care Excellence to investigate the added value of bone mineral density to fracture risk prediction.
- Investigates bone mineral density in both the commonly used, binary, and continuous format.
- Presents changes in calibration, discrimination, and reclassification to describe the added value of bone mineral density.
- Uses robustly collected data from Northern Denmark, with 3.2% missing data.
- As data is from a North Danish population, with at least one fracture risk factor, this limits generalisability of the results.

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Introduction

Osteoporosis causes over 8.9 million fractures worldwide, of which over 4.5 million occur in the USA and Europe, and account for 2.8 million disability adjusted life years (1). Further, 1.2 million disability adjusted life years are accounted for by hip fractures, which are projected to increase to 6 million by 2050 (2).

Given this burden, and treatment options for osteoporosis, identifying patients at risk of an osteoporotic fracture is high priority amongst health policymakers to reduce the risk of future fracture (3). Risk prediction tools have been developed to aid in the identification of patients at risk. For example, the Fracture Risk Assessment Tool (FRAX®) and QFracture® are commonly used to assess fracture risk in patients based on pre-defined risk factors.

Bone mineral density (BMD), a measurement used to aid diagnosis of osteoporosis, has also been identified as a fracture risk factor (4-7). Unlike some other fracture risk factors, treatment options (e.g. bisphosphonate medication) are available that reduces the fracture risk markedly when treatment is initiated based on low BMD.

English National guidelines (The National Institute for Health and Care Excellence (NICE)) for fracture risk assessment recommend treatment of osteoporosis to prevent fractures but have not included BMD as a mandatory risk factor for fracture risk prediction tools to incorporate (8). This is partly due to the lack of robust evidence and limited generalisability of current research, which has particularly focused on evaluating BMD in postmenopausal women evaluating the added value of BMD to existing fracture risk factors (5-7).

The National Institute of Clinical Health and Excellence also recognise this gap in the evidence and have recommended research to assess the added value of BMD as a risk factor in fracture risk assessment (9).

The aim of this study is to assess the value of BMD measurement in addition to the standard fracture risk factors used in the FRAX® risk model using a robustly collected prospective cohort.

Methods

This paper has been written in accordance to the TRIPOD checklist.

Patient and Public Involvement

Patients and the public were not involved in the development of this research question and were not involved in the design of this study.

Study Design and Data Source

A prospective cohort study was conducted using patients from the Aalborg University Hospital Record for Osteoporosis Risk Assessment (AURORA) dataset; patients were followed up using the National Patient Registry of Denmark.

The AURORA dataset consists of patients attending the Osteoporosis Clinic at Aalborg University Hospital after a referral from their primary care physician. A referral was offered to patients with at least one risk factor for osteoporosis (low BMI, previous fracture, parental hip fracture, smoking status, alcohol consumption, glucocorticoid use, rheumatoid arthritis, and secondary osteoporosis) or if they were aged 80 years and above. Further detail of the data collection has been described elsewhere (10). The Danish National Patient Registry which collects inpatient and outpatient data from all Danish hospitals, was linked to the AURORA dataset through unique patient identifiers

Ethics approval was given through the Region of North Jutland's from the Danish Data Protection Agency ("paraplyanmeldelse 2008-58-0028").

Cohort selection

Data collection for AURORA began 1st January 2010 and was collected for 3 years (up to 31st December 2012). Patients were included if they were aged 40-90 years; had a BMD T-score at the hip; and were not taking any osteoporotic preventing drugs or any bone sparing drugs for more than one year prior to baseline.

Primary Outcome

The primary outcome measure was an incident osteoporotic fracture during follow up (01/01/2012 to 01/01/2014); defined as a diagnosis of a fracture at the hip, spine, forearm, humerus, and pelvis. Fractures at these sites resulting from traffic, work, and sports related accidents were excluded from the study. Relevant fractures were identified in the Danish National Patient Registry, using the International Statistical Classification of Diseases, 10th Version codes (ICD-10 codes), which was developed using recognised database methodology for each fracture (11).

Fracture risk factors

Fracture risk factors, used in the FRAX® risk prediction model, were extracted at baseline. They were: age; gender; height (m); weight (kg); previous fracture; parental history of hip fracture, current smoking status; current alcohol consumption; glucocorticoid use (currently exposed for 3+ months); rheumatoid arthritis; and secondary osteoporosis (includes type I diabetes; osteogenesis imperfecta in adults; untreated, long standing hyperthyroidism; hypogonadism; premature menopause (<45 years); chronic malnutrition; malabsorption; and chronic liver disease).

Bone Mineral Density

DXA scans were performed by trained technicians using Hologic Discovery A (Bedford, MA, USA). A daily QC programme was in place and in vivo CV using repositioning of patients was <1%. Total hip BMD was used as region of interest. Bone mineral density was added to the fracture risk prediction model twice, firstly, as a continuously measured T-score value, and secondly, as a binary risk factor, dichotomised at/above T-score threshold for osteoporosis and below threshold, -2.5 in T-score (manufacturers' normal range using normal material from T Kelly et al (12)) based on World Health Organisation (WHO) classifications (13). Calculated T-scores were gender specific.

Statistical Analysis

A complete case analysis was performed on the data; 3.2% of data was missing. The AURORA dataset was split into two using recognised methodology (14); where a random number was assigned to patients and based on a cut off, two-thirds was used to derive the risk models, and the remaining third was used to validate them.

Model derivation

Three Cox proportional hazards models were developed for the primary outcome, using a complete case analysis on the derivation dataset:

- Model 1. Standard fracture risk factors only (without BMD)
- Model 2. Standard fracture risk factors (with binary BMD)
- Model 3. Standard fracture risk factors (with continuous BMD)

Graphical methods were used (log-log plots) to assess the proportional hazards assumption, and risk factors violating this assumption were added to the model as a time varying covariate.

Recognised methodology used in research studies was used to build the 3 risk prediction models (15, 16); the Kaplan Meier method was used to obtain 4-year fracture risk estimates for patients. Further detail on the conversion of the Cox proportional hazards models to risk prediction models has been provided in Supplementary Table 1.

Validation of Models

Four-year fracture risk was calculated from each model and the predictive performance of each risk prediction model was assessed by measures describing calibration, discrimination, and reclassification. These metrics were assessed using the validation cohort.

Calibration measures how well the predicted risk agrees with observed risk in the data. It plots the mean predicted and observed risk of fracture for each decile of predicted risk. The observed risk of fracture was derived from the 4 year Kaplan-Meier estimate. Good calibration indicates the predicted risk is close to the observed risk of the outcome.

Discrimination measures how well the risk prediction model differentiates between patients who have or have not observed the event in the study. This was quantified by the area under

the receiver operating characteristic (ROC) curve (AUC), given by Harrell's C-Index with higher values indicating better discrimination. Reclassification tables (17) measures movement between risk categories when adding a new risk factor. Threshold for treatment at 4 years was set at a fracture risk level of 8.5%; to be comparable to the treatment threshold of 20% at 10 years. This was presented by the total percent of patients reclassified (incorrectly and correctly), and also the Net Reclassification Index (NRI) (18, 19). The NRI gives the net calculation of the changes in the right direction and a higher NRI indicates a better reclassifying model. All analyses were carried out using Stata (version 12) (20). to occurrent on the second

Results

Characteristics of the data

The AURORA collected data on 7,912 patients; 1,795 patients were excluded comprising, 440 not aged between 40-90 years at baseline; 156 not having a recorded T-score value for the total hip at baseline; and 1,199 patients were taking anti-osteoporotic drug therapy for more than one year prior to baseline.

The study sample consisted of 6,117 patients; predominantly female (79.6%), and patients with a mean age of 62.9 (SD: 10.9) years. Two-thirds of this sample (n=4,093) was used for the derivation dataset and one-third (n=2,094) was used for the validation dataset. Table 1 presents the baseline characteristics of the study by derivation and validation dataset, and shows little difference between the datasets.

Patients in the derivation dataset had a median follow up time of 2.30 years [1.57, 2.99], and observed 318 (7.8%) osteoporotic fractures during follow up. Of these, 316 fractures were eligible for the analysis (2 patients had a fractures on or prior to baseline and were excluded). Patients contributed 9352.8 person years of observation, giving a total incidence rate of 337.87 per 10,000 person years (95% CI:302.60 to 377.25).

Fractures during follow up were predominantly found in the forearm (27.0%) and hip (17.9%). Higher fracture incidence rates were found in patients classed as osteoporotic, based on their T-score at both the total hip (809.73 per 10,000 person years (95% CI:641.68 to 1021.78)) and spine (L1-L4) (553.59 per 10,000 person years (95% CI:462.55 to 662.55)) (Supplementary Table 2).

Characteristic			Derivation (n=4,093)		Validation (n=2,024)	
			No	%	No	ĺ
Gender	Female		3,266	79.8	1,602	79
	Male		827	20.2	422	20
Osteoporotic (Hip DXA)	No		3,683	90.0	1,820	89
	Yes		410	10.0	204	1(
Osteoporotic Status (based on	Normal		1,886	46.1	927	43
UK guidelines)	Osteopenic		1,797	43.9	893	44
	Osteoporotic		410	10.0	204	1
Previous Fracture	No		2,935	71.7	1,423	70
	Yes		1,158	28.3	601	2
No of Previous Fractures	None		2,935	71.7	1,423	7
	1 fracture		862	21.1	467	2
	2-4 fractures		270	6.6	122	
	5+ fractures		26	0.6	12	
Parental History of Hip Fracture	No		2,755	67.3	1,359	6
	Yes		1,338	32.7	665	3
Current Smoking Status	other (non/ex)		3,182	77.7	1,529	7
	smoker		911	22.3	495	2
Alcohol Consumption	≤3 units per day		3,875	94.7	1,923	9
	>3 units per day		218	5.3	101	
Glucocorticoid Use	No		3,577	87.4	1,741	8
	Yes		516	12.6	283	1
Rheumatoid Arthritis	No		3,686	90.1	1,801	8
	Yes		407	9.9	223	1
Other Bone Affecting Disease	No		2,382	58.2	1,139	5
	Yes		1,711	41.8	885	4
Secondary Osteoporosis	No		3,438	84.0	1,689	8
	Yes		655	16.0	335	1
	By disease					
	Type 1 diabetes	No	4,010	98.0	1,981	9
		Yes	83	2.0	43	
	Osteogenesis	No	4,093	100	2,024	1
		Yes	0	0	0	
	Hyperthyroidism	No	4,089	99.9	2,023	9
		Yes	4	0.1	1	
	Malnutrition	No	4,090	99.9	2,023	9
		Yes	3	0.1	1	
	Chronic Liver Disease	No	4,006	97.9	1,979	9
		Yes	87	2.1	45	
	Menopause (Females only)**	No	853	26.1	405	2
		Yes	2,413	73.9	1,197	7

Table 1. Baseline characteristics of the derivation and validation	on datasets, including missing
data.	

	Premature Menopause (<45 years)***	No	1,904	78.9	941	78.6
		Yes	509	21.1	256	21.4
			Mean	SD	Mean	SD
Age (years)			62.9	10.9	63.0	11.0
Weight (kg)			72.1	15.5	72.2	15.9
	Missing		47	1.2	12	0.6
Height (m)			1.7	0.1	1.7	0.1
	Missing		131	3.2	61	3.0
BMI			26.4	5.0	26.4	5.1
	Missing		135	3.3	63	3.1
Hip DXA T-score			-1.1	1.1	-1.2	1.1

*out of patients with a fracture

**proportion out of respective number of females

***proportion out of respective number of females with menopause

Model development

The unadjusted analysis showed statistically significant association between BMD (continuous and binary) and osteoporotic fracture (HR=0.55; 95% CI: 0.50 to 0.61, p<0.001, HR=2.79; 95% CI: 2.11 to 3.67, p<0.001, respectively). Significant associations with fracture were also found with age (HR=1.03; 95% CI: 1.02 to 1.04, p<0.001), previous fracture (HR=3.38; 95% CI: 2.69 to 4.24, p<0.001), BMI (HR=0.97; 95% CI: 0.95 to 1.00, p=0.03), and gender (HR=0.73; 95% CI: 0.53 to 1.00, p=0.05). Further, a time-varying effect was found in patients with a previous fracture; hazard of a subsequent fracture was highest in the first year during follow up and decreased per year of follow up (p<0.001).

The adjusted analysis is presented in Table 2. Model 1 showed that of the standard risk factors, age and previous fracture were significantly associated with fracture; hazard of fracture increased by 2% per year increase in age (HR=1.024; 95% CI: 1.013 to 1.036); and increased almost 5 fold in patients with a previous fracture at time 0 years (HR=4.881; 95% CI: 3.336 to 7.078).

Hazard of fracture increased by 75% for patients classed as osteoporotic by their BMD score (Model 2, HR=1.745; 95% CI: 1.279 to 2.381). Hazard of fracture also decreased by 40% per SD improvement in BMD T-score (Model 3, HR=0.600; 95% CI: 0.524 to 0.686).

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		Adjusted Hazard Ratio (95% CI)			
Risk Factor		Model 1: Standard Risk Factors only	Model 2: Standard Risk Factors + BMD (categorical)	Model 3: Standard Risk Factors + BMI (continuous)	
Age (years)		1.024 (1.013 to 1.036)	1.019 (1.007 to 1.031)	1.007 (0.995 to 1.019	
Condor	Female	Ref	Ref	Ref	
Gelidei	Male	0.754 (0.544 to 1.044)	0.796 (0.573 to 1.104)	0.851 (0.613 to 1.18	
BMI		0.978 (0.954 to 1.002)	0.989 (0.965 to 1.013)	1.027 (1.000 to 1.05	
Dravious Francismo	No	Ref	Ref	Ref	
Previous Fracture	Yes (time = 0 years)	4.881 (3.336 to 7.078)	4.667 (3.214 to 6.778)	4.018 (2.763 to 5.842	
Demonstral Higtomy of Hig Encodyna	No	Ref	Ref	Ref	
Parental History of Hip Fracture	Yes	1.079 (0.834 to 1.397)	1.096 (0.847 to 1.419)	1.105 (0.854 to 1.43	
Comment Que alera	No	Ref	Ref	Ref	
Current Smoker	Yes	1.121 (0.852 to 1.475)	1.076 (0.817 to 1.417)	1.019 (0.774 to 1.342	
Alashal Consumption (>2 units/day)	No	Ref	Ref	Ref	
Alconol Consumption (>3 units/day)	Yes	1.414 (0.904 to 2.212)	1.440 (0.921 to 2.252)	1.459 (0.932 to 2.28	
Chassertissid Use	No	Ref	Ref	Ref	
Glucocorticola Use	Yes	1.080 (0.753 to 1.550)	1.052 (0.733 to 1.510)	1.038 (0.724 to 1.48	
Dhoumataid Anthritis	No	Ref	Ref	Ref	
Kileumatoid Artinitis	Yes	1.098 (0.731 to 1.650)	1.089 (0.725 to 1.637)	1.116 (0.742 to 1.67	
Sacandary Octoonarasis	No	Ref	Ref	Ref	
Secondary Osteoporosis	Yes	0.993 (0.729 to 1.354)	0.966 (0.708 to 1.317)	0.911 (0.667 to 1.242	
Osteoporotic	No	Ref	Ref	Ref	
	Yes	-	1.745 (1.279 to 2.381)	-	
Hip DXA T-score (SD)		-	-	0.600 (0.524 to 0.680	
Previous Fracture (TVC [*])		0.635 (0.489 to 0.826)	0.639 (0.492 to 0.830)	0.644 (0.495 to 0.837	

T rvals.

*TVC = time varying covariate, value is interaction effect and 95% CI.

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Model Validation

The 4-year predicted risk of fracture was calculated for all patients in the validation dataset; this was compared to the observed fracture outcome within the 4 year follow up.

Calibration and Discrimination

Calibration plots suggested some improvement when adding BMD measurement; particularly when including continuous BMD T-score measurement (Model 3; Supplementary Figure 1).

The largest change in discrimination was found when adding continuous BMD measurement to standard risk factors; Harrell's C-Index increased by 1.17% (Table 3). However, binary BMD measurement, as a measure for osteoporotic patients, was found to reduce Harrell's C-Index by -0.65%.

Table 3. Harrell's C-Index for Model 1, 2, 3, 4, and 5.

Model	Harrell's C-Index	Change in Harrell's C-Index (% change)*
Model 1 : Standard fracture risk factors only (without BMD)	0.764 (0.718 to 0.810)	-
Model 2 : Standard fracture risk factors only (with binary BMD)	0.759 (0.712 to 0.806)	-0.005 (-0.65%)
Model 3 : Standard fracture risk factors only (with continuous BMD)	0.773 (0.732 to 0.814)	0.009 (1.17%)
change is measures against Model 1.		

Reclassification

*All

Reclassification tables indicated that adding continuous BMD measurement may improve classification of patients into their correct risk categories. This was not found when adding binary BMD. Table 4 presents the reclassification table for Model 1 (standard fracture risk factors only) and Model 3 (standard risk factors with continuous BMD), using the 8.5% prespecified risk threshold.

Table 4. Risk Reclassification Table comparing Model 1 (standard fracture risk factors alone) to Model 3 (standard fracture risk factors with continuous BMD measurement), using a clinical 8.5% risk cut off.

			Model 3: SRF with continuous BMD			
			<8.5%	≥8.5%	Total	Total No.(%) Reclassified
		No	391	227		
		%	63.3%	36.7%		
Model 1: SRF	<8.5%	No. Events	5	9	618	227 (36.7%)
without BMD		No. Non events	386	218		
	C	Observed Event Rate	1.3%	4.0%		
		No	302	1,040		
		%	22.5%	77.5%		
-	≥8.5%	No. Events	10	121	1,342	302 (22.5%)
		No. Non events	292	919		
		Observed Event Rate	3.3%	11.6%		
	Total		693	1,267	1,960	529 (27.0%)

Of the 1,960 patients in the validation dataset, 27% (n=529) were reclassified into a different risk category when including continuous BMD into fracture risk prediction. Two percent (9/529) were found to be reclassified correctly into a higher risk group and 55% (292/529) were reclassified correctly into a lower risk group; indicating 22% (292/1342) of patients at high risk in Model 1, not accounting for BMD measurement, were no longer at high risk. The net reclassification improvement when adding continuous BMD to standard risk factors, was 0.03, which resulted from increased specificity (non-event NRI = 4%) and decreased sensitivity (event NRI: -1%) from Model 1 (Table 5).

Table 5. Summary of Net Reclassification Index (NRI) and Integrated Discrimination Index (IDI) for all comparisons between developed fracture risk prediction models.

Comparison	Event NRI	Non-Event NRI	Overall NRI
Model 1 vs. Model 2	-3.45%	2.09%	-0.01
Model 1 vs. Model 3	-0.69%	4.08%	0.03

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Discussion

Summary of Findings

Bone mineral density showed significant association with fracture risk with a 40% decrease for each SD rise in BMD. However, this resulted in small improvements in calibration, discrimination, and reclassification. The c-index estimate was slightly higher with continuous BMD but this increase is not conclusive given the width of the confidence intervals. Despite the limited improvement found of 1% in discrimination when adding continuous BMD, reclassification tables showed 57% of reclassified patients moving into their correct risk group through improved specificity. Importantly, no improvement was found when adding BMD in a binary format.

Our findings are consistent with and corroborate with current literature (7, 21, 22). Specifically, a study conducted in the Netherlands with 4 year follow up, investigating the added value of BMD for hip fractures risk, found modest improvement in predictability (21). Further, two more recent studies also indicated limited added value of BMD to fracture risk prediction (7, 22).

Strengths and Limitations

Answering Evidence gap

To our knowledge, this is the first study to investigate the added value of BMD in a binary and continuous format, to standard fracture risk factors. Further, it is based on a larger sample size than other studies investigating BMD in addition to FRAX (7, 21, 22). It helps inform the NICE research recommendation to assess the added value of BMD to routine fracture risk assessment in primary care (23). It further highlights that the more commonly used for treatment decision making, binary format of BMD resulted in a loss of predictability in fracture risk prediction; based on comparable measures for discrimination and reclassification

Robustness of Data

The prospective cohort was well populated with key standard risk factors recorded: BMI, smoking status and alcohol consumption, and personal and parental fracture history. Other than 3.2% of missing data for BMI, in 6,117 patients, complete data was collected for all risk factors (including BMD T-score recorded at the total hip). Further, the cohort was linked to a national robust electronic health records. This Danish National Patient Registry allowed for outcome fracture to be identified and also provided data on the mechanism for the fracture; this helped more accurately phenotype osteoporotic fractures.

Generalisability

The generalisability is affected in a few ways. Firstly, the findings are based on a Danish cohort. Secondly, AURORA data was collected from patients who presented to their doctor with at least one fracture risk factor and were referred to the osteoporosis clinic; this led to a biased study sample with a higher risk of a fracture and increased age. This could overestimate fracture risk amongst patients in a primary care setting.

Methodology

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Due to the increased age of the sample, death becomes a competing risk. However, information on death was not collected and could not be retrieved. This limited the analysis of the data as competing risks could not be accounted for which may again lead to an overestimation of fracture risk (24). However, as an independent study primarily assessing the added value of BMD through deriving and validating the fracture risk prediction models, this bias would be present in both analyses to compare derived risk models with and without BMD measurement. The FRAX risk algorithm has not yet been published, therefore FRAX estimates could not be

The FRAX risk algorithm has not yet been published, therefore FRAX estimates could not be directly calculated for the cohort. Instead, the FRAX risk model was recalibrated on the dataset with and without BMD added. Further, fracture outcomes in this study included pelvic fractures which are increasingly recognised as low trauma fragility fractures [(25)], and used BMD taken at the total hip instead of at the femur neck as it is the gold standard in Denmark (26).

Internal validation was performed to validate the derived risk prediction models. This may lead to over optimistic results of the performance of the risk models (14). To account for this limitation, a commonly practised method which randomly assigns patients to the derivation and validation datasets was used; further, a similar 1:2 ratio was also used to split the data (27-29).

The study had a 4 year follow up which is shorter than other recognised risk models. To account for this, we adapted the 20% clinical risk threshold for 10 year fracture estimates to 8.5% for 4 year fracture estimates, assuming that risk is constant over time (30, 31).

Traditional methodology assessing the added value to risk factors to existing risk prediction models are criticised to be insensitive to change, to lack interpretability (32-35). This was shown when finding a 1% change in Harrell's C-Index and overlapping confidence intervals between models, limiting the interpretability of results. Reclassification analysis was thus also used to provide more clinically interpretable results.

Clinical implications

The most notable clinical implication is the more routine use of BMD measurement for fracture risk assessment. Further, evidence suggests continuous BMD adds better predictability compared to the binary format.

Future Research

Further research is recommended to evaluate the added value of BMD to fracture risk prediction; in particular in addition to QFracture risk factors and using primary care routinely collected data. However, a brief interrogation into the Clinical Practice Research Datalink, a routinely collected UK primary care database, showed poor availability of BMD measurement in patient records, and thus, strong limitations to potential analyses. Less than 1% of patients had BMD recorded from a sample of 60,658 patients aged 40-90; not on any osteoporotic treatment; and with complete data for age, gender, BMI, smoking status, and alcohol consumption. Thus, prior to UK analysis, BMD recording in primary care databases needs to improve.

Methodologically, as well as assessing the added value of BMD to standard risk factors, we should also explore the option to replace existing fracture risk factors with the BMD measurement; this has rarely been explored in the literature but should be considered in future analyses. We also recommend research to investigate the added value of BMD in a potentially more natural, 3 group format of BMD (osteopenic, normal, osteoporotic).

In addition, further research is recommended to develop current methodology used to assess the added value of BMD to provide more clinically relevant results, such as cost implications; and to allow for better comparability between new risk factors with respect to their added value, thus improving decision making.

Conclusion

Continuous BMD marginally improves fracture risk assessment. Importantly, this was only found when using continuous BMD measurement for osteoporosis. It seems that prediction models for fragility fracture risk may be improved only marginally, using present risk factor assessment and evaluations. It is suggested that future focus should be on additional risk factors and on the development of more clinically relevant methodology to assess the added value of a new risk factor.

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Supplementary Information

Beta coefficients from each Cox regression model were used to create each fracture risk prediction model.

Once all 5 models were finalised, their beta coefficients were used to create 5 risk prediction models and calculate risk of fracture for each patient, using the following general equation:

$$\widehat{risk} = 1 - S_0(t)^{exp(\sum_{i=1}^p \beta_i X_i - \sum_{i=1}^p \beta_i \overline{X}_i)}$$

Where $S_0(t)$ is the baseline survival rate at follow up time, t(for this example, a follow up time of 10 years will be used); beta (β_i) are the regression coefficients for each included risk factor in the model (i); X_i is the observed data value for each risk factor; \overline{X}_i is the corresponding mean for each risk factor; and \mathbf{p} is the total number of risk factors included in the model. Table A1 shows the formula for each risk prediction model explicitly.

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where $\sum_{i=1}^{p} \beta_i X_i =$ 0.0237745*age+-0.2826461*gender+-0.0225011*BMI+1.585278*previous fracture- 0.0762559*parental hip fracture+0.1138883*smoking status+0.0773898*glucocortic 0.3465287*alcohol consumption+0.0936966*rheumatoid arthritis+ -0.0069432*secondary osteoporosis+-0.4535108*(previous fracture*time) where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ 0.0237745*mean age+-0.2826461*mean gender+-0.0225011*mean BMI+ 1.585278*mean previous fracture+0.0762559*mean parental hip fracture+ 0.1138883*mean smoking status+0.0773898*mean glucocorticoid use+ 0.3465287*mean alcohol consumption+0.0936966*mean rheumatoid arthritis+ -0.0069432*mean secondary osteoporosis+-0.4535108*mean (previous fracture*time) where $\sum_{i=1}^{p} \beta_i X_i =$ 0.0186627*mean 10.228784*condert 0.0112651*PMI+1.540550*previous fracture
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-0.0346885*mean secondary osteoporosis+0.5568944*mean osteoporosis+
-0.4481145*mean (previous fracture*time)

Supplementary Table 1. Risk equations to calculate 4 year risk based on patient characteristics for each

Model 3	where $\sum_{i=1}^{p} \beta_i X_i =$ 0.0071931*age+-0.1615582*gender+0.0268478*BMI+1.39069*previous fracture+ 0.1000272*parental hip fracture+0.0192416*smoking status+0.0374944*glucocorticoid us 0.3774416*alcohol consumption+0.1097646*rheumatoid arthritis+ -0.0932063*secondary osteoporosis+-0.5110986*t-score+-0.4404955*(previous fracture*time) where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ 0.0071931*mean age+-0.1615582*mean gender+0.0268478*mean BMI+
Model 3	0.0071931*age+-0.1615582*gender+0.0268478*BMI+1.39069*previous fracture+ 0.1000272*parental hip fracture+0.0192416*smoking status+0.0374944*glucocorticoid us 0.3774416*alcohol consumption+0.1097646*rheumatoid arthritis+ -0.0932063*secondary osteoporosis+-0.5110986*t-score+-0.4404955*(previous fracture*time) where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ 0.0071931*mean age+-0.1615582*mean gender+0.0268478*mean BMI+
Model 3	0.1000272*parental hip fracture+0.0192416*smoking status+0.0374944*glucocorticoid us 0.3774416*alcohol consumption+0.1097646*rheumatoid arthritis+ -0.0932063*secondary osteoporosis+-0.5110986*t-score+-0.4404955*(previous fracture*time) where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ 0.0071931*mean age+-0.1615582*mean gender+0.0268478*mean BMI+
Model 3	0.3774416*alcohol consumption+0.1097646*rheumatoid arthritis+ -0.0932063*secondary osteoporosis+-0.5110986*t-score+-0.4404955*(previous fracture*time) where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ 0.0071931*mean age+-0.1615582*mean gender+0.0268478*mean BMI+
Model 3	osteoporosis+-0.5110986*t-score+-0.4404955*(previous fracture*time) where $\sum_{i=1}^{p} \beta_i \overline{X}_i =$ 0.0071931*mean age+-0.1615582*mean gender+0.0268478*mean BMI+
Model 3	where $\sum_{i=1}^{p} \beta_i \bar{X}_i =$ 0.0071931*mean age+-0.1615582*mean gender+0.0268478*mean BMI+
Model 3	0.0071931*mean age+-0.1615582*mean gender+0.0268478*mean BMI+
	-
	1.39069*mean previous fracture+0.1000272*mean parental hip fracture+
	0.0192416*mean smoking status+0.0374944*mean glucocorticoid use+
	0.3774416*mean alcohol consumption+0.1097646*mean rheumatoid arthritis+
	-0.0932063*mean secondary osteoporosis+-0.5110986*mean t-score+
	-0.4404955*mean (previous fracture*time)

Risk Factor			Ľ	Derivation	G S Validation		
		No of incident cases	Total Person years	Crude Incidence Rate per 10000 person years (95% CI)	No of incident cases	127Appii 20 orfuses rel	Crude Incidence Rate per 10000 person years (95% CI)
	40-49	17	1169.9	145.31 (90.33 to 233.74)	12		215.15 (122.19 to 378.84)
	50-59	70	2534.7	276.17 (218.49 to 349.07)	33	to te	251.71 (178.95 to 354.06)
	60-69	93	3062.9	303.63 (247.79 to 372.06)	42	uper an	288.87 (213.48 to 390.88)
Age Category	70-79	83	1906.0	435.46 (351.17 to 539.98)	49	d dan d dan	511.11 (386.29 to 676.26)
	80-89	52	652.7	796.75 (607.13 to 1045.59)	16		460.56 (282.15 to 751.77)
	90-99	1	26.6	376.51 (53.04 to 2672.85)	-	hing,	-
Osteoporotic - Hip	No	245	8475.9	289.05 (255.03 to 327.61)	123		295.31 (247.48 to 352.40)
	Yes	71	876.8	809.73 (641.68 to 1021.78)	29	ain ⁴ 63.5	625.28 (434.52 to 899.78)
Osteoporotic - Spine	No	191	7025.8	271.86 (235.91 to 313.28)	111	g g 4756	319.37 (265.16 to 384.67)
	Yes	119	2149.6	553.59 (462.55 to 662.55)	39		358.08 (261.63 to 490.10)
	Female	266	7417.5	358.61 (318.01 to 404.40)	129		350.56 (295.00 to 416.59)
Jender	Male	50	1935.3	258.36 (195.82 to 340.88)	23	ec na	242.36 (161.05 to 364.71)
Parental History Hip	No	220	6281.5	350.24 (306.88 to 399.71)	118	00000000000000000000000000000000000000	379.58 (316.92 to 454.64)
Fracture	Yes	96	3071.3	312.57 (255.90 to 381.79)	34	1520-2	223.66 (159.81 to 313.02)
		1	(Table o	continues on the next page]	1	gence Biblio	

 Page 25 of 28

			D	erivation	Validation		
Risk Factor cont.		No of incident cases	Total Person years	Crude Incidence Rate per 10000 person years (95% CI)	No of incident cases	Grotal Gresson Greats	Crude Incidence Rate po 10000 person years (95% CI)
Current Smoker	No	240	7279.1	329.71 (290.53 to 374.18)	103		293.19 (241.70 to 355.65
Current Smoker	Yes	76	2073.7	366.5 (292.71 to 458.90)	49	ated 188	439.16 (331.91 to 581.07
Alcohol Consumption	No	293	8875.9	330.11 (294.39 to 370.15)	140		318.2 (269.63 to 375.53)
more than 3 units per day	Yes	23	476.9	482.33 (320.52 to 725.83)	12	oade uperi xt an	523.66 (297.39 to 922.09
Glucocorticoid Use (3	No	279	8184.5	340.89 (303.15 to 383.33)	132		330.57 (278.73 to 392.06
months)	Yes	37	1168.3	316.7 (229.47 to 437.11)	20	a Mir	314.57 (202.95 to 487.59
Menopause	No	68	1962.8	346.44 (273.15 to 439.39)	29		312.19 (216.94 to 449.24
	Yes	198	5454.7	362.99 (315.79 to 417.24)	100	A 17509	363.52 (298.82 to 442.23
Premature Menopause (<45 years)	No	280	8175.4	342.49 (304.64 to 385.05)	127		314.97 (264.69 to 374.81
	Yes	36	1177.4	305.76 (220.56 to 423.89)	25	g. <u>ສ</u> ສາງ ອີກ	418.92 (283.07 to 619.97
	No	289	8876.1	325.59 (290.14 to 365.38)	141	S 3670	322.87 (273.75 to 380.82
BMI - low (<18.5)	Yes	11	187.0	588.16 (325.72 to 1062.04)	4	niar 24 5	322.63 (121.09 to 859.62
	No	289	8457.8	341.70 (304.49 to 383.45)	139	e e 1351	336.15 (284.66 to 396.94
Rheumatoid Arthritis	Yes	27	895.0	301.69 (206.90 to 439.93)	13	, 2025	263.29 (152.88 to 453.43
			[Table c	ontinues on the next page]		at Agence Bibliogra s.	

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]	Derivation		ll889a	alidation
Risk Factor cont.		No of incident cases	Total Person years	Crude Incidence Rate per 10000 person years (95% CI)	No of incident cases	B B Cotal Cotal B C Cotal B Cotal B Cotal B Cotal B Cotal B Cotal B Cotal B Cotal B Cotal B Cotal B Cotal B Cotal B Cotal B C Cotal B C Cotal B C C Cotal B C Cotal B Cotal Cotal B C Cotal B C Cotal B C Cotal B C Cotal B C Cotal C Cotal C C C C C COT C COT C C COT C C COT C C CO	Crude Incidence Rate per 10000 person years (95% CI)
Secondary Osteoporosis	No	262	7846.5	333.9 (295.83 to 376.89)	122	11,24 18,00 19,00 10,14	316.60 (265.12 to 378.07)
	Yes	54	1506.2	358.51 (274.58 to 468.10)	30	184.De neme ated t	386.89 (270.51 to 553.34)
Description Freedom	No	144	6832.0	210.77 (179.01 to 248.17)	63		189.79 (148.26 to 242.95)
Flevious Macture	Yes	172	2520.8	682.32 (587.61 to 792.31)	89	ct an an	679.69 (552.18 to 836.64)
	None	144	6832.0	210.77 (179.01 to 248.17)	63	d dat d dat	189.79 (148.26 to 242.95)
Previous Fracture, detail	1 fracture	105	1919.6	546.99 (451.76 to 662.29)	52	a Am HCH258	495.36 (377.47 to 650.07)
	2-4 fractures	57	557.9	1021.62 (788.04 to 1324.45)	33	5) 5) 10236 <mark>%</mark>	1397.28 (993.37 to 1965.44)
	5+ fractures	10	43.2	2311.27 (1243.59 to 4295.60)	4	A tra	1701.81 (638.72 to 4534.31)
Total		316	9352.8	337.87 (302.60 to 377.25)	152		328.38 (280.11 to 384.96)

316 9352.8 337.87 (302.60 to 377.25) 152 a628.8 gc and similar technologies. and similar technologies. eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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Supplementary Figure 1 Predicted and Observed risk by 10th of predicted risk for each risk prediction model in the derivation dataset.

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Title and abstract	item		Checklist item	Γaι
	4	Div	Identify the study as developing and/or validating a multivariable prediction model, the	
litte	1	D;V	target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
			Explain the medical context (including whether diagnostic or prognostic) and rationale	
Background	3a	D;V	for developing or validating the multivariable prediction model, including references to	5
and objectives			existing models.	
	3b	D;V	validation of the model or both	5
Methods				
	42	D·V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry	F
Background and objectives ethods Source of data Participants Outcome Predictors Sample size Missing data Statistical analysis methods Risk groups Development vs. validation esults Participants Participants Model development Model development Model specification Model performance Model-updating iscussion	чα	D, V	data), separately for the development and validation data sets, if applicable.	
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable,	6
			Specify key elements of the study setting (e.g. primary care secondary care general	
	5a	D;V	population) including number and location of centres.	6
Participants	5b	D;V	Describe eligibility criteria for participants.	6
	5c 🚽	D;V	Give details of treatments received, if relevant.	-
O (6a	D:V	Clearly define the outcome that is predicted by the prediction model, including how and	e
Outcome	6h	,. 	When assessed.	
	do	U,V	Clearly define all predictors used in developing or validating the multivariable prediction	
Drediets	7a	D;V	model, including how and when they were measured.	6/
Predictors	76	עים	Report any actions to blind assessment of predictors for the outcome and other	
	70	U,V	predictors.	
Sample size	8	D;V	Explain how the study size was arrived at.	-
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single	7
-	10a	Р	Describe how predictors were handled in the analyses	6
	104		Specify type of model, all model-building procedures (including any predictor selection).	0/
Statistical analysis methods Risk groups Development vs. validation Results	10b	D	and method for internal validation.	
	10c	V	For validation, describe how the predictions were calculated.	6
methods	10d	D:V	Specify all measures used to assess model performance and, if relevant, to compare	7/
	100		multiple models.	_
Risk arouns	10e	V D·V	Provide details on how risk groups were created, if done	1
Development	11	D, V	For validation, identify any differences from the development data in setting, eligibility	_
vs. validation	12	V	criteria, outcome, and predictors.	1
Results				
	120		Describe the flow of participants through the study, including the number of participants	0
	13a	D;V D;V	with and without the outcome and, if applicable, a summary of the follow-up time. A	5
			Describe the characteristics of the participants (basic demographics, clinical features,	
Participants	13b		available predictors), including the number of participants with missing data for	9
			predictors and outcome.	
	13c	V	For validation, show a comparison with the development data of the distribution of	10/
	140	D	Important variables (demographics, predictors and outcome).	(
Model	14d	_	If done, report the unadjusted association between each candidate predictor and	
development	14b	D	outcome.	1
	150	П	Present the full prediction model to allow predictions for individuals (i.e., all regression	Su
Model	ıJd	U	coefficients, and model intercept or baseline survival at a given time point).	d
specification	15b	D	Explain how to the use the prediction model.	Su
Model		_		d
performance	16	D;V	Report performance measures (with CIs) for the prediction model.	13/
Model undating	17	V	If done, report the results from any model updating (i.e., model specification, model	10
would-upualing	17	v	performance).	15
Discussion			Discuss any limitations of the study (such as percentative equals for events per	
Limitations	18	D;V	predictor missing data)	15/
	4.5	.,	For validation, discuss the results with reference to performance in the development	<u> </u>
Interpretation	19a	V	data, and any other validation data.	1
merpretation	19h	D·V	Give an overall interpretation of the results, considering objectives, limitations, results	15
1	100	D,V	from similar studies, and other relevant evidence.	1.3/
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	1
Supplementary			Provide information about the availability of supplementary resources, such as study	Su
information	21	D;V	protocol, Web calculator, and data sets.	do
internation				

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml