Ten-year follow-up of fracture risk in a systematic population-based screening program: the risk-stratified osteoporosis strategy evaluation (ROSE) randomised trial

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eClinicalMedicine 2024;71: 102584
Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102584

Summary

Background Osteoporotic fractures pose a growing public health concern. Osteoporosis is underdiagnosed and undertreated, highlighting the necessity of systematic screening programs. We aimed to evaluate the effectiveness of a two-step population-based osteoporotic screening program.

Methods This ten-year follow-up of the Risk-stratified Osteoporosis Strategy Evaluation (ROSE) randomized trial tested the effectiveness of a screening program utilizing the Fracture Risk Assessment Tool (FRAX) for major osteoporotic fractures (MOF) to select women for dual-energy x-ray absorptiometry (DXA) scan following standard osteoporosis treatment. Women residing in the Region of Southern Denmark, aged 65–80, were randomised (single masked) into a screening or a control group by a computer program prior to inclusion and subsequently approached with a mailed questionnaire. Based on the questionnaire data, women in the screening group with a FRAX value ≥15% were invited for DXA scanning. The primary outcome was MOF derived from nationwide registers. ClinicalTrials.gov: NCT01388244, status: Completed.

Findings All randomised women were included February 4, 2010–January 8, 2011, the same day as approached to participate. During follow-up, 7355 MOFs were observed. No differences in incidences of MOF were identified, comparing the 17,072 women in the screening group with the 17,157 controls in the intention-to-treat analysis (IRR 1.01, 0.95; 1.06). However, per-protocol, women DXA-scanned exhibited a 14% lower incidence of MOF (IRR 0.86, 0.78; 0.94) than controls with a FRAX value ≥15%. Similar trends were observed for hip fractures, all fractures, and mortality.

Interpretation While the ROSE program had no overall effect on osteoporotic fracture incidence or mortality it showed a preventive effect for women at moderate to high risk who underwent DXA scans. Hence the overall effect might have been diluted by those who were not at an intervention level threshold risk or those who did not show up for DXA. Using self-administered questionnaires as screening tools may be inefficient for systematic screening due to the low and differential screening uptake.

Funding INTERREG and the Region of Southern Denmark.

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Keywords: Fracture; FRAX; Osteoporosis; Population-based screening; Prevention

Research in context

Evidence before this study

We searched MEDLINE for papers published until September 2023 to identify studies evaluating the effectiveness of systematic osteoporotic screening regarding fracture incidence. The search terms included "screening," "osteoporosis," "fractures, bone", and "osteoporotic fractures", and were restricted to randomized controlled trials and meta-analyses to ensure a high level of evidence. We also searched MEDLINE to identify papers describing the incidence/prevalence of osteoporotic fractures and the social burden. We further checked the literature list of identified papers. An unstructured search was performed to identify methodological papers, and clinicians involved in the project provided literature on Danish guidelines regarding osteoporotic treatment.

The ten-year findings of the ROSE trial presented in this paper should be understood in the context of other studies conducted in the interim period, aiming to screen for high fracture risk. Osteoporosis, primarily affecting postmenopausal women, results in costly low-trauma fractures. Only a minority of individuals at high risk receive anti-osteoporotic treatment. Systematic screening programs using fracture risk assessment tools and DXA scans can potentially decrease incidents and disparities of osteoporotic fractures. We established the ROSE randomized trial in 2010, which utilized a risk assessment tool (FRAX) based on self-reported questionnaire data to select participants for DXA scans in women aged 65–80. Only two other randomized controlled trials have assessed the effectiveness of systematic screening programs for osteoporosis based on FRAX: The SCOOP trial from UK and the Dutch SOS trial. Compared with ROSE, the study populations were slightly older and recruited via general practitioners rather than population registers. In 2019, Merlijn et al. conducted a meta-analysis, combining data from ROSE, SCOOP, and SOS studies with a maximum follow-up of five years. The analysis revealed a decrease in osteoporotic fractures, including hip fractures. Notably, the ROSE study's estimates were derived from a per-protocol analysis of women providing questionnaire data, which differed from the intention-to-treat analysis that showed no effect. Nevertheless, there is an evidence-gab concerning the effectiveness beyond five years.

Added value of this study

Identifying high-risk individuals becomes significant only if treatment uptake is sufficient and enduring. Thus, the ultimate evaluation criterion for a population-based intervention rests on its protracted influence on life over decades. To this end, the ten-year follow-up of the ROSE trial is pivotal as it is the most extensive study, critically evaluating the long-term and sustained effectiveness of a systematic population-based screening program, aligning with the FRAX tool.

Utilization of the Danish Nationwide registers allowed for an extended and nearly complete follow-up and ensured high-quality fracture data. Our intention-to-treat analyses, encompassing all randomized women, revealed no overall screening effect on fracture incidence. Importantly, the term "intention-to-treat" does not imply an actual intention to intervene in women with an FRAX score under 15%. Therefore, about 70% of the screened population were not DXA scanned. Per-protocol, we found an indication of a protective effect in women with moderate to high fracture risk, i.e., in women meeting the criterion randomized and consenting to DXA versus no DXA offered.

Implications of all the available evidence

Given its low and differential participation rate, FRAX, relying on self-administered questionnaires, may not be the most efficient tool for population-based screening programs. Further research is warranted to enhance fracture risk prediction and screening uptake, e.g., through digital detection tools.

Introduction

Osteoporotic fractures represent a growing global public health concern, affecting an estimated 9.0 million individuals annually. Western countries have the highest fracture rates Worldwide,[1] with Denmark exhibiting one of the highest rates for hip fractures.[2] Osteoporotic fractures affect predominantly postmenopausal women, and over one in four women aged 50+ are expected to experience an osteoporotic fracture in their remaining lifetime.[3] Osteoporosis, characterized by diminished bone mineral density (BMD), increases bone fragility, leading to low-trauma fractures associated with considerable pain, morbidity, and mortality.[3,4] In Europe, osteoporotic fractures are estimated to account for 2 million disability-adjusted life years (DALYs) annually incurring a substantial economic burden of €56 billion per year. Given the aging global population, these social and economic costs are expected to increase further.[5]

Timely identification of osteoporosis and fracture risk, followed by prompt initiation of appropriate anti-osteoporotic medication (AOM) is pivotal to reduce the fracture incidence. Unfortunately, osteoporosis often goes undiagnosed and untreated as it is often

asymptomatic until a fracture occurs.[6,7] In Denmark and other countries, an unstructured case-finding strategy identifies individuals at elevated risk of osteoporotic fractures, referring them for assessment, including dual-energy x-ray absorptiometry (DXA) scans to measure BMD.[6–8] To enhance the prediction, the University of Sheffield released the fracture risk prediction tool (FRAX®) in 2008,[9] which estimates the individual ten-year probability of osteoporotic fractures based on clinical risk factors.[3] Combining FRAX with BMD measurement may prove effective in identifying high-risk individuals for targeted treatment before they have a fracture. Nonetheless, the systematic implementation of FRAX remains limited, with a paucity of data for the most efficient and acceptable screening approach for osteoporosis in real-life settings.[10–12]

To address this evidence gap, in 2010, the Risk-stratified Osteoporosis Strategy Evaluation (ROSE) trial was initiated to investigate a two-step osteoporosis screening program in a population-based sample of women aged 65–80 years. This program utilizes FRAX via a self-administered questionnaire to select participants for DXA scans, following standard osteoporosis treatment according to the Danish national guidelines.[13,14] In the ROSE five-year follow-up, we found no overall effect on fracture incidence in the intention-to-treat analysis. In pre-specified analyses comprising only women with an adequate risk to warrant DXA scan, i.e., at FRAX >15%, the ROSE program demonstrated a reduction in the fracture incidence.[15] A meta-analysis of three trials, including ROSE, assessed the effectiveness of systematic screening programs that included FRAX and indicated a protective effect on osteoporotic fracture incidence.[10] However, evidence for a follow-up period longer than five years still needs to be provided.[10,11] This study's primary aim is to assess the effectiveness of the ROSE program in reducing the incidence of major osteoporotic fractures (MOF) over a ten-year follow-up period, with secondary objectives of evaluating its impact on the incidence of hip fractures, all fractures, and mortality.

Methods

Study design

The ROSE trial was a single masked (participants), population-based, randomised controlled trial conducted in the Region of Southern Denmark (https://classic.clinicaltrials.gov/ct2/show/NCT01388244), which has been described in other publications.[13,15–17] The trial was approved by the Regional Committee on Health Research Ethics for Southern Denmark (jr.nr S-20090127) and Danish Data Protection Agency before inclusion of any participant.

Participants, randomisation and masking

Women born 1930–1946 residing in the Region of Southern Denmark in February 2010 were identified using the Danish Civil Registration System Register.[18] Of the 117,217 residents, 34,229 were randomly selected to participate in the ROSE trial. Before invitation to participate, the women were randomised in a 1:1 ratio into either a screening or control group. Randomisation was stratified based on one-year age groups and 22 areas of residence using a computerized random number program. A computer program also divided the women into 158 groups, consecutively invited at different waves between February 2010 and June 2011. The participants were unaware of their group assignment at the time of inclusion.

The Regional Committee on Health Research Ethics approved data collection through questionnaires, wherein the women could consent for subsequent contact. Women in the screening group invited for DXA received oral and written information before signing informed consent. According to Danish legislation, registry data on all Danes may be collected without the individual's consent.

Procedures

At inclusion, all participants aged 60–80 years received a mailed letter containing a self-administered questionnaire that included 25 FRAX items to calculate the ten-year probability of MOF. At this stage no exclusion criteria was applied. Women in the screening group with a FRAX value of ≥15% were subsequently invited to undergo an assessment that included a DXA scan. Women declining interest in DXA scans or with self-reported use of AOM or a diagnosis of osteoporosis were excluded. Between March 2010 and April 2013, BMD of the lumbar spine (L1–L4) and right total hip was measured using DXA at four hospitals in the region. After DXA scan, the results were communicated to the women and their general practitioners (GPs) via a letter. If osteoporosis was identified, expressed as a BMD T-score of ≤−2.5 SD, the woman was advised to see her GP and discuss treatment according to the Danish national guidelines, which recommend AOM treatment in patients with at least one clinical risk factor and a T-score below −2.5 SD.[14] Neither group was informed about FRAX results.[13] Thus, initiation of treatment was not part of the study design, and it was also possible for participants in the control group to obtain DXA scans or AOM through their GP (off-protocol examination or treatment).

We utilized the personal identification numbers assigned to all citizens of Denmark to link individual participants in the ROSE trial with various national registers. The Danish Civil Registration System Register[18] provided demographic data on the women, while registers at Statistics Denmark provided socioeconomic data.[19] The Danish National Patient Register,[20] which maintains records of all inpatient and outpatient hospital contacts in Denmark since 1995, provided information on diagnosis codes and procedures at Danish

Hospitals. The Danish National Prescription Registry,[21] established in 1995, provided information on prescriptions redeemed from Danish pharmacies.

Characteristics at inclusion obtained from the National registers included age, country of origin based on country of birth or citizenship, marital status, disposable family income, retirement pension, and highest obtained educational level. To assess comorbidity, we utilized the ICD-10 codes recorded in the Patient Register visits up to ten years prior to inclusion and classified them according to the Charlson Comorbidity Index (CCI) following the approach by Quan et al.[22] We assessed the number of redeemed co-medications (utilizing the first three ATC characters) in the year preceding inclusion obtained from the Prescriptions Registry. The Prescriptions Registry also provided information on redeemed oral AOM (including anabolics and parenterally administered antiresorptives) based on the ATC codes: G03XC01, M05BA01-4, M05BA06-8, M05BB01, M05BB03, M05BX03-4, M05BX06, and H05AA02. We assessed AOM during hospital contacts and DXA scans (both scans according to the ROSE protocol and off-protocol scans) derived from the Patient Register using procedure codes, see Supplementary material.

Outcomes

The primary outcome was MOF incidence calculated from the number of MOF during the ten-year follow-up period obtained from the Patient Register.[20] MOF was defined as a hip, clinical vertebrae, wrist, or humerus fracture, recorded as either a primary or secondary diagnosis code. Specifically, the ICD-10 codes for MOF included: S720, S721, S722 (hip), S320, T08, S220, S221, S120, S121, S122 (clinical vertebral), S525, S526 (wrist), S422 and S423 (humerus). Secondary outcomes were incidence of hip fractures and all potential osteoporotic fractures (ICD-10 codes: S12, S22, S32, S42, S52, S72, S82, and T08), except fractures of fingers, toes, skull, or face. For a hip fracture to be included in any of the outcomes, both an ICD-10 code and a surgical code (KNFB* or KNFJ4-9) needed to be recorded within a maximum of seven days apart. Hospital contacts needed to be at least one day apart for fractures with different fracture sites to be counted as separate incidents. To differentiate incident fractures within the same fracture site, we used a grace period of 90 days between hospital contacts.

Post hoc, we also assessed date of death during follow-up obtained from the Danish Civil Registration System as a secondary outcome.

Statistical analysis

The initial sample size calculation estimated that the study would need about 35,000 women. This estimation relied on the anticipated response rate (80%), the anticipated prevalence of FRAX ≥15% (76%), the anticipated acceptance of DXA scans (80%), the expected incidence of osteoporosis among those invited for DXA scans (50%), the likelihood of women diagnosed with osteoporosis consulting general practitioners (80%), and the assumed reduction in fracture risk by 25% due to treatment. Furthermore, power calculations demonstrated a follow-up period of at least three to five years would provide 80% power to demonstrate effectiveness.[13]

We compared women in the screening group with women in the control group in three sub-populations comprising (Sub-populations are illustrated in the Trial-profile, Fig. 1):

(A) Women randomised and approached with a mailed questionnaire, representing the intention-to-treat analysis;
(B) Women who returned the questionnaire with sufficient information to calculate a FRAX value, representing the per-protocol 1 analysis; and
(C) Women with FRAX ≥15% who were either DXA-scanned (screening group, actually receiving the intervention) or left unscanned (control group), representing the per-protocol 2 analysis.

Baseline characteristics of the study population were presented as frequencies for categorical variables and as medians with interquartile-range for continuous variables.

The women were followed until the occurrence of the first of the following events: death, emigration, or date for ten-year follow-up. The inclusion date was defined as the date the questionnaire was mailed or returned for non-responders and responders, respectively. Women in the DXA screening group underwent scanning a median of 195 days after the inclusion date, leading to left truncation. To accommodate this delayed entry, we defined the entry date for the DXA intervention group as the scan date, while the entry date was imputed based on the median days between inclusion and scan for the remaining women. Thus, fractures before entry date and women who emigrated or died before the entry date were not included in the risk-sets estimating the fracture incidences.

We calculated fracture rates as incident fractures per person-time during the follow-up. The ten-year cumulative incidence of the first fracture was estimated using the Aalen-Johansen estimator, treating death as a competing risk.[23] For death, the ten-year cumulative incidence was calculated as 1-Kaplan Meier. We estimated the Incidence Rate Ratio (IRR) based on fracture count, applying Negative Binomial Regression, which is suitable for handling over-dispersed count data. We incorporated time-intervals between entry, fracture incidents, and censoring in the regression model. When evaluating the risk of death, we utilized Cox Regression to estimate hazard ratios (HRs) and the proportional hazard assumptions were met.

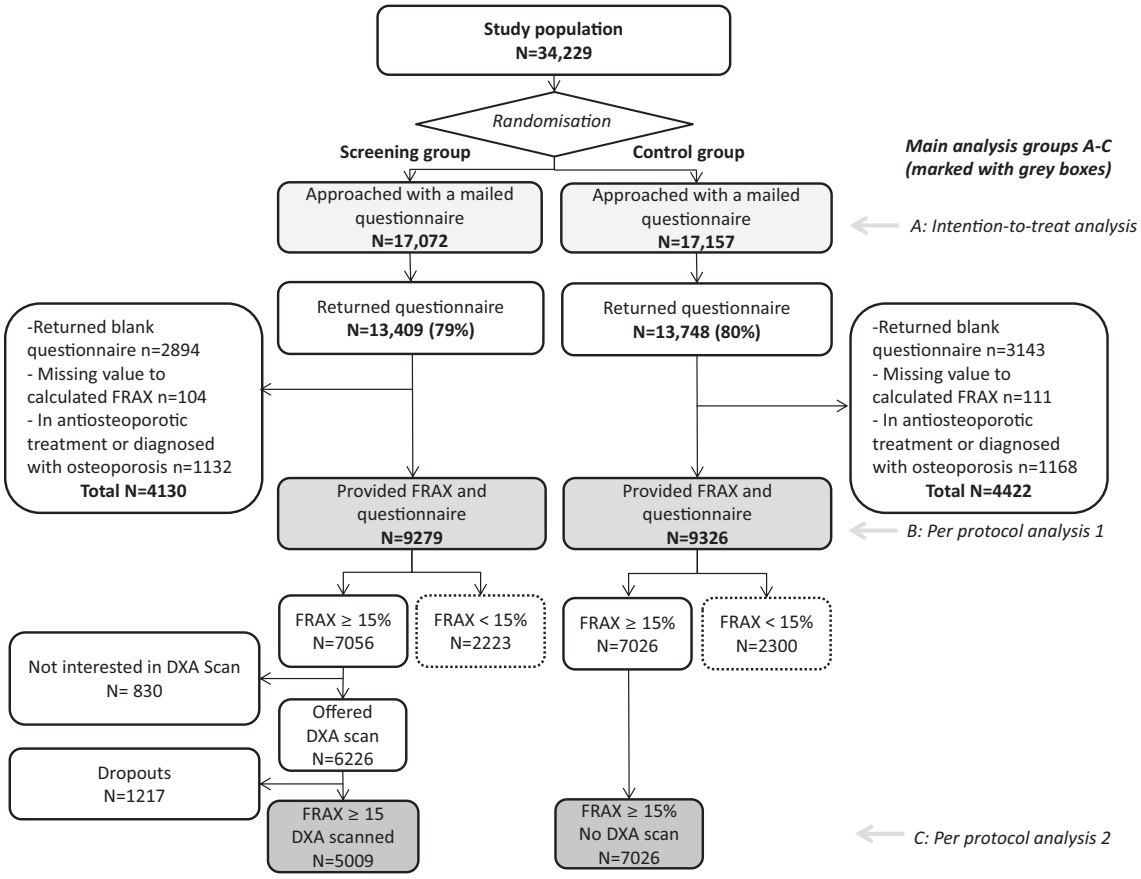

Fig. 1: **Trial-profile**.

Estimates were adjusted for age (included as cubic splines) and CCI (0, 1, ≥2) and presented with 95% confidence intervals (95% CI).

We performed subgroup-analyses to investigate group differences.

(Sub1-Sub2) We assessed the ROSE program's effectiveness across age groups (65–69, 70–74, and 75+) and fracture history (no prior MOF, <3 years before inclusion, and ≥3 years before) by performing stratified analyses and examining interaction-terms;

(Sub3) In time-to-event analyses, we compared AOM initiation in scanned vs. controls using different FRAX cut-offs (FRAX >15%, >18%, >20%, >22%, >25%). We calculated cumulative incidences using the Aalen-Johansen approach[23] and estimated overall HRs using Cox Regression. Although the proportional-hazard assumption was violated, we reported overall HRs without slitting the analysis-time, as we were interested in the combined effect after a ten-year follow-up period.

We performed sensitivity-analyses to assess findings' robustness with varying analytical methods or measure definitions:

(Sen4) To assess if the observed effects on osteoporotic fractures were primarily due to hip fractures, we excluded hip fractures from the measures of MOF and all fractures.

(Sen5) We evaluated fracture incidences in DXA-scanned compared to controls using various FRAX cut-offs ranging from >15% to >40%;

(Sen6) We used Fine–Gray Regression, accounting for competing risk of death, to evaluate the impact of the ROSE program on the occurrence of the first osteoporotic fracture during follow-up;

(Sen7) To evaluate the consequences of not considering delayed entry, we conducted analyses in which women entered the risk-sets upon receiving the questionnaire;

(Sen8) We performed analyses additionally adjusted for baseline characteristics that showed significant differences between the screening and control group to assess if these imbalances could account for an observed screening effect; (Sen9–Sen10) To examine potential selection bias, we compared characteristics of screened women who underwent DXA scans with those who declined or did not attend the scan. Subsequently, we applied an Inverse Probability Weight (IPW)[24,25] in the regression model when comparing DXA scans with controls to adjust for possible selection bias. The IPW

was calculated using logistic regression based on the propensity of being included in the analysis among women in the screening group with a FRAX value of ≥15%, and the IPW was only assigned to the screening group in the regression model of the screening effect; (Sen11) We assessed the screening effect in women with a FRAX value of ≥15% without excluding women from the screening group who declined scanning or dropped out. This enabled us to assess whether the observed association in women meeting the FRAX threshold for intervention is diluted when those from the screening group who did not undergo DXA scanning are included.

(Sen12) Finally, we compared ROSE participants from the control group with the background population of women residing in the Region of Southern Denmark who were not invited to participate in regard to AOM initiation, off-protocol DXA scans, and MOF, identified in the registers. The ROSE controls and the women not invited were age-matched (1:1), and the uninvited women entered the analyses on the same date as their matched ROSE control. This comparison aimed to explore whether ROSE trial invitation and participation affected fracture risk awareness and subsequent behaviour, potentially introducing bias of the effectiveness of the ROSE program toward the null. We used the Aalen-Johansen[23] estimator to calculate cumulative incidences, Cox Regression to estimate overall hazard ratios, and Negative Binomial Regression to estimate IRR. To make the groups comparable, women with a record of AOM or MOF in the registers before the index date were excluded from analyses of AOM and MOF, respectively.

The trial is registered at ClinicalTrials.gov (NCT01388244). All statistical analyses were carried out in StataMP 18 (64-bit).

Role of the funding source

The study was supported by INTERREG (4A JNR 08/4177), the Region of Southern Denmark (JNR 08/8133), and Odense University Hospital (JNR 11/5761). The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Results

Fig. 1 shows the Trial-profile. The ROSE trial encompassed 17,072 women in the screening group and 17,157 women in the control group approached to participate and included from February 4, 2010, to January 8, 2011, at age 65–80. All were eligible for the intention-to-treat analysis (Analysis A) where we assessed the women based on their assigned groups regardless of whether they completed the ROSE program. Around 80% (n = 27,157/34,229) responded to the ROSE questionnaire, of which approximately 70% (n = 9279 screening group; n = 9326 control group) provided sufficient data for calculating the FRAX value and were eligible for Analysis B. In the screening group, 24% (n = 2223/9279) women had a FRAX <15% and therefore were not offered further assessment. Among women in the screening group with a FRAX value of ≥15% who were offered DXA, 29% (n = 2047/7056) were not interested in a scan or dropped out. Thus, Analysis C included 5009 women who underwent DXA scanning per-protocol, and, concurrently, 7026 controls with a FRAX value of ≥15%.

In Analysis A, which included all women approached for participation, baseline characteristics were similar between the screening group and controls, except for lower prevalence of comorbidities in the screening group. In Analysis B, comprising women with adequate FRAX data, the screening group exhibited a slightly higher age, lower family income, lower proportion with a BMI ≤19, and a lower prevalence of comorbidities than the control group. In Analysis C, the 5009 women DXA-scanned exhibited several differences when compared to the control group. On average, they had a lower: age, family income, prevalence of comorbidities, median FRAX (MOF) score, prevalence of smokers, and proportion with a BMI ≤19. Conversely, they had a higher: prevalence of being married, being recipients of retirement pensions, and having a history of fractures before their inclusion in the study, Table 1.

Findings regarding the primary outcome MOF were as follow in Analysis A: Among women approached for participation, 2956 in the screening group (n = 17,072) had at least one MOF and a total of 3690 MOF incidents during follow-up, corresponding to an incidence rate of 2.64 (95% CI: 2.56; 2.73) per 100 person-years. In controls (n = 17,157), 2967 had at least one MOF, 3665 MOF incidents, and an incidence rate of 2.61 (95% CI: 2.53; 2.70) per 100 person-years, Table 2 top. The ten-year cumulative incidences of the first MOF incident were similar comparing the screening group with controls, Fig. 2 and Table 2 top. Moreover, in Analysis A, we found no effect of the ROSE program after a ten-year follow-up on the incidence rate of MOF (adjusted IRR 1.01 (95% CI: 0.95; 1.06)), Table 3 top.

Similarly, no noticeable differences were observed between the screening and control group regarding MOF incidences in Analysis B, which included women providing sufficient data for calculating the FRAX value, Table 3 middle.

In Analysis C, the incidence rate of MOF was 2.07 (95% CI: 1.94; 2.20) per 100 person-years in women DXA-scanned as part of the ROSE protocol and 2.46 (95% CI: 2.34; 2.59) per 100 person-years in controls with similar FRAX value, Table 2 lower part. Fig. 2 reveals a lower cumulative incidence of MOF in DXA-scanned vs. controls in Analysis C. Specifically, 15.97 (95% CI: 13.95; 16.02) DXA-scanned and 17.32 (95% CI: 16.44; 18.22) controls out of 100 women got a MOF during the ten-year follow-up, Table 2 lower part.

	A		B		C	
	Approached for participation		Provided FRAX and questionnaire		FRAX ≥15%: DXA-scanned vs control group	
	Screening	Control	Screening	Control	Screening	Control
	N = 17,072	N = 17,157	N = 9279	N = 9326	N = 5009	N = 7026
Information from national registers						
Age						
Median [Q1; Q3]	71.0 (68.0; 76.0)	71.0 (68.0; 76.0)	70.0 (67.0; 74.0)	70.0 (67.0; 74.0)	**71.0 (68.0;75.0)**	**72.0 (69.0;75.0)**
65–69	6451 (37.8%)	6571 (38.3%)	4206 (45.3%)	4319 (46.3%)	**1735 (34.6%)**	**2231 (31.8%)**
70–74	5279 (30.9%)	5302 (30.9%)	2829 (30.5%)	2866 (30.7%)	1896 (37.9%)	2658 (37.8%)
75+	5342 (31.3%)	5284 (30.8%)	**2244 (24.2%)**	**2141 (23.0%)**	**1378 (27.5%)**	**2137 (30.4%)**
Marital status[a]						
Married	9851 (57.7%)	9781 (57.0%)	5959 (64.2%)	5891 (63.2%)	**3200 (63.9%)**	**4237 (60.3%)**
Widow	4697 (27.5%)	4749 (27.7%)	2139 (23.1%)	2193 (23.5%)	**1238 (24.7%)**	**1874 (26.7%)**
Divorced	1984 (11.6%)	2052 (12.0%)	975 (10.5%)	1002 (10.7%)	474 (9.5%)	736 (10.5%)
Unmarried	536 (3.1%)	572 (3.3%)	206 (2.2%)	240 (2.6%)	**97 (1.9%)**	**179 (2.5%)**
Missing	4 (0.0%)	3 (0.0%)	. (.%)	. (.%)	. (.%)	. (.%)
Education[a]						
Lower secondary	9410 (56.1%)	9557 (56.7%)	4502 (49.2%)	4473 (48.6%)	2428 (49.1%)	3519 (50.8%)
Upper secondary	5030 (30.0%)	5031 (29.8%)	3071 (33.6%)	3133 (34.1%)	1680 (34.0%)	2248 (32.5%)
Post-secondary	2321 (13.8%)	2272 (13.5%)	1571 (17.2%)	1593 (17.3%)	833 (16.9%)	1158 (16.7%)
Missing	311 (1.8%)	297 (1.7%)	135 (1.5%)	127 (1.4%)	68 (1.4%)	101 (1.4%)
Country of origin[a]						
Danish	16,440 (96.3%)	16,548 (96.5%)	8986 (96.8%)	9062 (97.2%)	4856 (96.9%)	6799 (96.8%)
Other Western	437 (2.6%)	405 (2.4%)	248 (2.7%)	209 (2.2%)	132 (2.6%)	181 (2.6%)
Non-western	191 (1.1%)	201 (1.2%)	45 (0.5%)	55 (0.6%)	21 (0.4%)	46 (0.7%)
Missing	4 (0.0%)	3 (0.0%)	. (.%)	. (.%)	. (.%)	. (.%)
Family income per year (disposable)[a]						
Low tertile	5754 (33.7%)	5654 (33.0%)	**2751 (29.7%)**	**2572 (27.6%)**	1437 (28.7%)	1954 (27.8%)
Middle tertile	5651 (33.1%)	5757 (33.6%)	3011 (32.5%)	3065 (32.9%)	1608 (32.1%)	2242 (31.9%)
High tertile	5661 (33.2%)	5743 (33.5%)	>3510	3689 (39.6%)	>1960	2830 (40.3%)
Missing	6 (0.0%)	3 (0.0%)	<3	. (.%)	<3	. (.%)
Retirement pension[a]						
Yes	>855	>845	587 (6.3%)	575 (6.2%)	**250 (5.0%)**	**282 (4.0%)**
No	16,210 (95.0%)	16,307 (95.1%)	8692 (93.7%)	8751 (93.8%)	**4759 (95.0%)**	**6744 (96.0%)**
Missing	<3	<2	. 0 (0%)	0 (0%)	0 (0%)	0 (0%)
CCI						
=0	**13,237 (77.5%)**	**13,146 (76.6%)**	**7546 (81.3%)**	**7450 (79.9%)**	**4056 (81.0%)**	**5516 (78.5%)**
=1	1480 (8.7%)	1495 (8.7%)	617 (6.6%)	660 (7.1%)	358 (7.1%)	535 (7.6%)
≥2	**2355 (13.8%)**	**2516 (14.7%)**	**1116 (12.0%)**	**1216 (13.0%)**	**595 (11.9%)**	**975 (13.9%)**
Co-medication						
Median [Q1; Q3]	5.0 (2.0; 8.0)	5.0 (2.0; 8.0)	4.0 (2.0; 7.0)	4.0 (2.0; 7.0)	5.0 (2.0; 7.0)	4.0 (2.0; 7.0)
Information from questionnaires						
FRAX (MOF)						
Median [Q1; Q3]	–	–	20 [15; 27]	20 [15; 27]	**22 [15; 29]**	**23 [18; 29]**
FRAX (hip)						
Median [Q1; Q3]	–	–	6.7 [3.9; 11]	6.6 [3.9; 11]	**8.1 [5.6; 13]**	**8.5 [5.8; 13]**
Previous fracture	–	–	981 (10.6%)	919 (9.9%)	**717 (14.3%)**	**917 (13.1%)**
Parental hip fracture	–	–	1235 (13.3%)	1248 (13.4%)	944 (18.9%)	1245 (17.7%)
Current smoker	–	–	1321 (14.2%)	1338 (14.4%)	**735 (14.7%)**	**1166 (16.6%)**
Use of oral glucocorticoids	–	–	224 (2.4%)	228 (2.4%)	158 (3.2%)	227 (3.2%)
Rheumatoid arthritis	–	–	479 (5.2%)	498 (5.3%)	324 (6.5%)	481 (6.9%)

(Table 1 continues on next page)

	A		B		C	
	Approached for participation		Provided FRAX and questionnaire		FRAX ≥15%: DXA-scanned vs control group	
	Screening	Control	Screening	Control	Screening	Control
	N = 17,072	N = 17,157	N = 9279	N = 9326	N = 5009	N = 7026
(Continued from previous page)						
Condition related to secondary osteoporosis	–	–	1833 (19.8%)	1847 (19.8%)	1238 (24.7%)	1766 (25.1%)
Alcohol ≥3 units daily	–	–	99 (1.1%)	111 (1.2%)	59 (1.2%)	98 (1.4%)
Body mass index ≤19 kg/m^2	–	–	**251 (2.7%)**	**312 (3.4%)**	**156 (3.1%)**	**299 (4.3%)**

Data are presented as frequencies (n (%)) for binary and categorical variables and as medians with interquartile rang (median [Q1; Q3]) for continuous variables. Bold estimates indicate statistical significant differences (p-value<0.05) assessed by Chi^2 test for binary and categorical variables and the Wilcoxon Rank Sum test for continues variables. A, intention-to-treat analysis; B, per-protocol analysis 1; C, per-protocol analysis 2. CCI, Carlson's comorbidity index. [a]The distribution of the variable is calculated among those without missing data, while the percentage of individuals with missing data is calculated based on participants in the entire group.

Table 1: **Baseline characteristics obtained from national registers and supplied questionnaires of women participating in ROSE study.**

Adjusted analyses showed that the DXA-scanned women had a 14% reduced incidence rate of MOF (adjusted IRR 0.86, 95% CI: 0.78; 0.94) compared with controls, Table 3 lower part.

Analyses of the secondary outcomes: hip fractures, all fractures, and death revealed similar findings. No screening effect was observed in Analysis A, including all women approached for participation, or in Analysis B, including women who provided adequate FRAX data, Table 3 top and middle. However, in Analysis C, comparing DXA-scanned women with controls, the adjusted IRR was 0.82 (95% CI: 0.70; 0.97) for hip fractures and 0.84 (95% CI: 0.77; 0.92) for all fractures, and the adjusted HR was 0.85 (95% CI: 0.78; 0.92) for death, Table 3 lower part.

In post hoc analyses, we found the reduced incidence rate of hip fracture in women DXA-scanned (Analysis C) appeared mainly to be restricted to women aged ≥75 years. The adjusted IRR for hip fracture was 0.68 in this group with a significant interaction between the ROSE program and age (p = 0.019), Table Sub1. While analyses stratified by fracture history suggested that the reduced fracture incidence of the ROSE program primarily is found in women without prior fractures, test for interaction could not confirm an effect modification, Table Sub2.

Post hoc, we further found that the impact of the screening program was most prominent in the first year, with 27.2% of the DXA-scanned group initiating treatment, in contrast to 1.0% in the control group meeting the same FRAX criterion of ≥15%. The proportion of AOM users increased in both groups during follow-up, reaching 43.7% in the DXA-scanned group and 20.2% in the control group by the tenth year. Notably, even after ten years, the control group had not reached the treatment initiation level observed in the DXA-scanned group within the first year. The overall relative difference remaining consistently at 70% across various FRAX cut-offs, Table Sub3.

Findings from sensitivity-analyses were as follows. Excluding hip from the measures of fractures, showed negligible changes in the estimates for MOF, Table Sen4. Moreover, examining different FRAX cut-offs indicated that the gain of the ROSE program did not increase with FRAX-score cut-off higher than 15%, Table Sen5. Examining time to first fracture, exploring the Fine–Gray Regression (Table Sen6), and performing Negative Binomial Regression without adjustment for delayed entry (Table Sen7) yielded results consistent with the primary analyses. Furthermore, the estimates remained unchanged in analyses additionally adjusted for baseline characteristics that were not equally distributed between the screening group and controls, Table Sen8. Descriptive analyses revealed notable differences concerning baseline characteristics between women in the screening group with a FRAX value of ≥15% who did not undergo DXA scanning and those who did, Table Sen9. Nevertheless, including an IPW into the regression model of Analysis C, accounting for variations caused by selection, maintained the reduced incidence of fracture and death in DXA scanned compared with controls, Table Sen10. By refraining from excluding women who did not undergo DXA scanning, the IRRs become closer to one although they still pointed towards a reduction in incidence in the screening group among women with a FRAX value of ≥15%, Table Sen11. Finally, we found that controls in the ROSE trial had a higher AOM uptake than age-matched women from the Region of Southern Denmark who were not invited for participation. However, no overall differences were observed regarding to off-protocol DXA scans or MOFs after 10 years follow-up, Table Sen12.

Discussion

This population-based randomised controlled trial evaluated the effectiveness of the ROSE program after ten-year follow-up that consisted of a self-administered questionnaire followed by a DXA scan offered to women with a moderate or high risk of osteoporotic

	Screening					Control				
	First incident N	Total incidents N	Person-years at risk (median [Q1; Q3])	Rate per 100 person-years (95% CI)	10-year cumulative incidence of first fracture[a] (95% CI)	First incident N	Total incidents N	Person-years at risk (median [Q1; Q3])	Rate per 100 person-years (95% CI)	10-year cumulative incidence of first fracture[a] (95% CI)
A										
Approached for participation (Screening n = 17,072; control n = 17,157)										
MOF[b]	2956	3690	139,738.8 (9.5 [8.6; 9.5])	2.64 (2.56; 2.73)	17.78 (17.13; 18.45)	2967	3665	140,183.7 (9.5 [8.8; 9.5])	2.61 (2.53; 2.70)	17.42 (16.85; 18)
Hip	1081	1154	139,738.8 (9.5 [8.6; 9.5])	0.83 (0.78; 0.87)	6.48 (6.08; 6.89)	1012	1080	140,186.7 (9.5 [8.8; 9.5])	0.77 (0.73; 0.82)	5.98 (5.63; 6.34)
All fractures[c]	3830	6224	139,738.7 (9.5 [8.6; 9.5])	4.45 (4.34; 4.57)	23.16 (22.28; 24.05)	3872	6157	140,183.6 (9.5 [8.8; 9.5])	4.39 (4.28; 4.50)	22.7 (22.07; 23.34)
Death	4727	4727	139,738.8 (9.5 [8.6; 9.5])	3.27 (3.17; 3.36)	27.21 (26.54; 27.9)	4779	4779	140,191.9 (9.5 [8.8; 9.5])	3.26 (3.17; 3.35)	27.02 (26.36; 27.7)
B										
Provided FRAX and questionnaire (Screening n = 9279; control n = 9326)										
MOF[b]	1363	1686	80,715.6 (9.5 [9.1; 9.5])	2.09 (1.99; 2.19)	15.01 (14.22; 15.81)	1455	1774	81,114.7 (9.5 [9.5; 9.5])	2.19 (2.09; 2.29)	15.63 (14.89; 16.38)
Hip	416	445	80,715.6 (9.5 [9.1; 9.5])	0.55 (0.50; 0.60)	4.58 (4.14; 5.04)	431	459	81,114.7 (9.5 [9.5; 9.5])	0.57 (0.52; 0.62)	4.64 (4.22; 5.08)
All fractures[c]	1816	2831	80,715.6 (9.5 [9.1; 9.5])	3.51 (3.38; 3.64)	20.11 (19.09; 21.15)	1906	2950	81,114.7 (9.5 [9.5; 9.5])	3.64 (3.51; 3.77)	20.44 (19.62; 21.27)
Death	1671	1671	80,715.6 (9.5 [9.1; 9.5])	2.04 (1.95; 2.14)	18.02 (17.24; 18.83)	1709	1709	81,114.7 (9.5 [9.5; 9.5])	2.05 (1.96; 2.15)	17.95 (17.19; 18.75)
C										
FRAX ≥15%: DXA-scanned vs control group (screening n = 5009; control n = 7026)										
MOF[b]	733	910	44,052.2 (9.3 [9.0; 9.7])	2.07 (1.94; 2.20)	14.97 (13.95; 16.02)	1213	1483	60,310.1 (9.5 [9.5; 9.5])	2.46 (2.34; 2.59)	17.32 (16.44; 18.22)
Hip	227	239	44,052.2 (9.3 [9.0; 9.7])	0.54 (0.48; 0.62)	4.62 (4.04; 5.25)	392	418	60,310.1 (9.5 [9.5; 9.5])	0.69 (0.63; 0.76)	5.61 (5.08; 6.17)
All fractures[c]	978	1488	44,052.2 (9.3 [9.0; 9.7])	3.38 (3.21; 3.55)	20.1 (18.84; 21.39)	1570	2444	60,310.1 (9.5 [9.5; 9.5])	4.05 (3.89; 4.22)	22.37 (21.39; 23.36)
Death	841	841	44,052.2 (9.3 [9.0; 9.7])	1.91 (1.78; 2.04)	16.98 (15.96; 18.06)	1468	1468	60,310.1 (9.5 [9.5; 9.5])	2.36 (2.24; 2.49)	20.42 (19.49; 21.38)

The number of first incidents, total incidents and person-years at risk during the follow-up period are presented. The rates per 100 person-years were estimated based on the total number of incidents during the follow-up period and presented with 95% confidence intervals (95% CI). The 10-year cumulative incidence of first fracture was estimated using the Aalen-Johansen estimator taking competing risk due to death into account, while the 10-year cumulative incidence of death was calculated as 1-Kaplan Meier. A = intention-to-treat analysis (n = 17,072 screening group, n = 17,157 control group), B = per-protocol analysis (n = 9279 Screening group, n = 9326 control group) 1, C = per-protocol analysis 2 (n = 5009 screening group, n = 7026 control group). [a]The cumulative incidences were presented per 100 person-years. [b]MOF is the primary outcome and includes hip, clinical vertebral, wrist, or humerus fractures. [c]Includes all fractures (ICD10 codes: S12, S22, S32, S42, S52, S72, S82, and T08), except fractures of fingers, toes, skull, or face.

Table 2: **Osteoporotic fracture incidences and deaths during follow-up.**

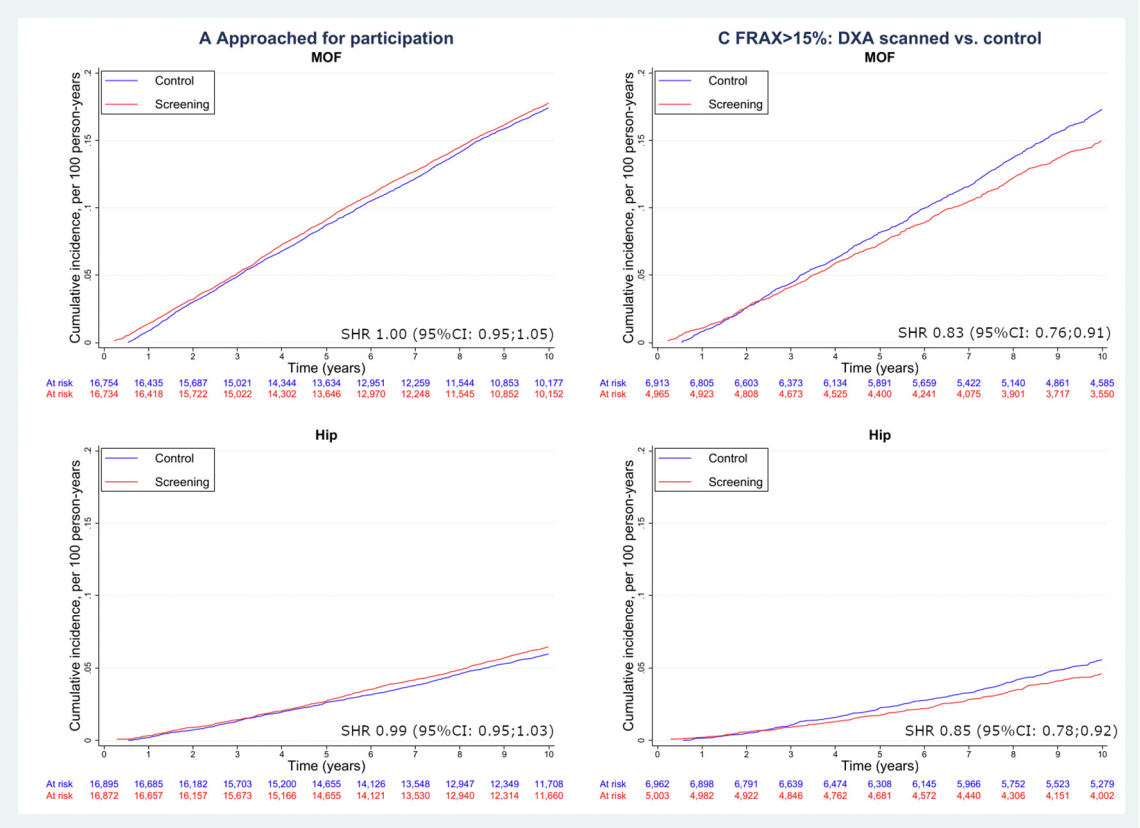

Fig. 2: **Cumulative incidence function of first osteoporotic fracture**. The cumulative incidence function was plotted using the Aalen-Johansen estimator taking into account competing risk due to death. Subhazards ratios (SHR) were estimated using Fine Gray Regression and presented with 95% confidence intervals (95% CI).

fractures. In our intention-to-treat analysis (Analysis A), we found no overall effect of the screening program on the primary outcome, MOF or any of the secondary outcomes. Per-protocol (Analysis C), we found that women who underwent DXA scans and were advised to see their GP's for treatment according to national guidelines, had a decreased incidence of MOF, hip fractures, all fractures, and mortality compared to women not scanned whose FRAX value was ≥15%. Our findings suggested that the ROSE program primarily benefits women aged 75 years or older, typically classified as high-risk individuals. On the other hand, we found no increased gain of the ROSE program with an increased FRAX cut-off higher than 15%. Post hoc analyses demonstrated a noteworthy finding: the ROSE program strongly affects AOM initiation in women assessed with moderate to high fracture risk.

Several factors that can have affected the findings towards no effect should be taken into consideration: 1) The effect of the DXA scan is anticipated to be diluted in Analysis A, as the intention-to-treat analysis did not signify an intervention for women with a FRAX score<15%, a substantial proportion of the population. Therefore, per-protocol, we planned to compare women with a FRAX score ≥15% who were either DXA-scanned or not offered a scan (Analysis C), as an effect is expected in this group. 2) The control group is not entirely "screening-naïve" since some women might have attended their GP's potentially leading to DXA scans and treatment aligning with the typical case-finding approach in Denmark. Consequently, our results showed a weakened effect of the ROSE program (Analysis C) in analyses restricted to women with prior fractures, who likely have undergone DXA scans and received treatment before inclusion. 3) Women in the control group were exposed to the study invitation and a questionnaire crucial for FRAX estimation. This could have heightened their osteoporosis awareness and prompted off-protocol consultations with GPs. Our findings support this, with control women in the ROSE trial initiating AOM treatment earlier than the background population of uninvited women.

Around 80% responded to the ROSE questionnaire, but less than 70% provided sufficient data for FRAX calculation, leading to baseline characteristic imbalances between the screening and control groups. Additionally,

	MOF[a]		HIP		All fractures[b]		Death	
	IRR (95% CI)	IRR[c] (95% CI)	IRR (95% CI)	IRR[c] (95% CI)	IRR (95% CI)	IRR[c] (95% CI)	HR (95% CI)	HR[c] (95% CI)
A								
Approached for participation (Screening n = 17,072 vs. control n = 17,157)	1.01 (0.96; 1.06)	1.01 (0.95; 1.06)	1.07 (0.98; 1.17)	1.07 (0.98; 1.16)	1.01 (0.96; 1.06)	1.01 (0.96; 1.06)	1.00 (0.96; 1.05)	1.00 (0.96; 1.04)
B								
Provided FRAX and questionnaire (Screening n = 9279 vs. control n = 9326)	0.95 (0.88; 1.03)	0.95 (0.88; 1.02)	0.97 (0.85; 1.12)	0.96 (0.84; 1.10)	0.96 (0.89; 1.03)	0.96 (0.89; 1.03)	1.00 (0.93; 1.07)	0.99 (0.93; 1.07)
C								
FRAX ≥15%: DXA-scanned (n = 5009) vs control group (n = 7026)	**0.84 (0.76; 0.92)**	**0.86 (0.78; 0.94)**	**0.78 (0.66; 0.92)**	**0.82 (0.70; 0.97)**	**0.83 (0.76; 0.90)**	**0.84 (0.77; 0.92)**	**0.80 (0.74; 0.88)**	**0.85 (0.78; 0.92)**

Incidence Rate Ratios (IRR) were estimated using Negative Binomial Regression including the outcome according to the number of fracture incidences. The model incorporated time intervals between entry, fracture incidents and censoring. Hazard ratios (HR) for death were estimated using Cox Regression. The estimates are presented with 95% confidence intervals (95% CI). Bold estimates indicate statistical significant estimates based on the calculated 95% CI. A = intention-to-treat analysis (n = 17,072 screening group, n = 17,157 control group), B = per-protocol analysis (n = 9279 Screening group, n = 9326 control group) 1, C = per-protocol analysis 2 (n = 5009 screening group, n = 7026 control group). [a]MOF is the primary outcome and includes hip, clinical vertebral, wrist, or humerus fractures (S720, S721, S722, S320, T08, S220, S221, S120, S121, S122, S525, S526, S422 and S423). [b]Includes all fractures (ICD10 codes: S12, S22, S32, S42, S52, S72, S82, and T08), except fractures of fingers, toes, skull, or face. [c]IRR/HR adjusted for age and Carlson's comorbidity index.

Table 3: **Risk of osteoporotic fractures and death according the ROSE screening program.**

29% of women offered a DXA scan declined or did not attend their scheduled appointment. These women tended to be older, more frequently lived alone, and exhibited a higher risk profile for osteoporotic fractures compared to women who underwent DXA scans.[16] Disparities in participation within population-based screening programs concerns the program's effectiveness. Sensitivity analyses supported that the screening's effect weakened when those who chose not to participate in the DXA scan were not excluded, possibly reflecting the natural effect of the screening program. On the other hand, the analyses indicated the screenings programs effectiveness if enough individuals accept DXA scanning. It raises questions about how we can design stratified and differentiated programs that target the group with the highest risk but lowest health literacy. Both practical and health issues must be taken into consideration.[16,17] Furthermore, self-administered questionnaires may present barriers to participation among specific high-risk individuals. Therefore, it is worthwhile to consider alternative screening approaches that are built upon automated digital detection tools, such as the Fracture Risk Evaluation Model, FREM, or the Fracture Liaison Service, FLS, which hold the potential to enhance the screening uptake.[26]

Our ten-year follow-up findings align with the five-year follow-up of the ROSE trial,[15] despite methodological differences and extended follow-up. In the previous five-year follow-up, time to the first fracture was assessed using the Fine–Gray Regression. In contrast, in this ten-year follow-up, we chose a Negative Binomial Regression model, including fractures as a count variable, because survival analysis may underestimate cumulative fracture incidences due to fractures' common occurrence and time-dependent modification of future fracture risk after the first fracture. Additionally, a higher count of fractures might impact the patients more. Despite these different analytical approaches, analyses showed similar results. We also employed a delayed entry approach in the present study, which did not impact the findings.

The SCOOP five-year follow-up trial[11] found no effect on overall osteoporotic fracture incidences or mortality when evaluating an osteoporosis screening program comprising FRAX followed by a DXA scan in British women aged 70–85. Yet, screened women started AOM treatment earlier and exhibited a reduced incidence of hip fractures (HR 0.72, 95% CI: 0.59; 0.89) compared to controls. These findings were derived from intention-to-treat analyses, in which we observed no similar trends. The SCOOP trial recruited women through their GPs, randomising them after consent was obtained and they had responded a self-administered questionnaire. Additionally, the SCOOP trial used the FRAX probability for hip, and selection for treatment was based on both femoral neck BMD and FRAX. This setup diverged from the ROSE trial, which may have implications for

the findings. In contrast, the SOS trial, a randomised population-based screening program assessing FRAX in combination with BMD measures in 11,032 Dutch women aged 65–90 years, showed no fracture or mortality reduction in the intention-to-treat analyses.[12] A meta-analysis combining findings from the SOS, ROSE, and SCOOP studies revealed an overall reduction in osteoporotic fractures, including hip fractures, with no impact on mortality. The meta-analysis also demonstrated the clinical relevance of osteoporotic fracture screening, showing that the number needed to screen to prevent one osteoporotic fracture is 272.[10]

A major strength of the ROSE trial is the large pragmatic population-based randomised control trial-design. This design allowed us to assess the effectiveness of combining FRAX with BMD in a real-world setting and compare it to standard care in a representative sample of older women. Additionally, it is a strength that we randomised participants into the screening and control groups prior to their inclusion, using national register data to identify women residing in the Region of Southern Denmark. This procedure minimized bias caused by confounding and selection in the intention-to-treat analyses.

Moreover, the FRAX questionnaire has been comprehensively tested and validated in various populations. It has the advantage of being easily accessible, which makes it a suitable tool for population-based screening programs.[3] Another important strength is that the Danish Nationwide registers ensured nearly complete follow-up of the participants and provided high-quality data on sociodemographic factors[19] and fracture diagnoses, which have a positive predicted value close to 90%.[27,28]

A potential limitation of this study is the non-random and considerable proportion of women who were approached for participation but either chose not to participate or withdrew from the study, which can have introduced selection bias into the estimates of the per-protocol analyses. Reassuringly, sensitivity analyses with additional adjustments and with inclusion of IPWs indicated that the reduced incidence rate of fractures and death comparing the DXA-scanned with controls (Analysis C) was not explained by bias introduced by the selection process. However, we must consider the possibility that missing or incomplete measures may have limited the effectiveness of the bias correction. In addition, the Charlson Comorbidity Index measurement may have been inadequate for accounting for comorbidities, as we were unable to identify diagnoses outside secondary care in the registers. To address this limitation, we conducted sensitivity analyses to adjust for the number of redeemed co-medications as a proxy for comorbidities outside hospital settings. Another potential limitation is that comorbidities were included as fixed covariates in the analyses, not accounting for the changing health status during follow-up. Finally, the FRAX algorithm may lack essential factors such as falls and diabetes mellitus. It should be further investigated whether adding additional clinical risk factors improves the prediction of the FRAX[29] or whether reducing the length of the questionnaire improves data completeness.

In conclusion, the ten-year follow-up of this population-based, randomised controlled trial provided the opportunity to evaluate the long-term and sustained impact of the ROSE program, which included a two-step systematic screening program for women aged 65 to 80. Intention-to-treat analyses revealed no overall effect of the ROSE program on the incidence of MOF, hip, all fractures, or mortality after a ten-year follow-up. However, per-protocol analyses indicated a preventive effect of the ROSE program in women with moderate to high fracture risk, particularly in the oldest age group. The extended follow-up aligns with FRAX's ten-year timeline, but its reliability diminishes over time due to the dynamic nature of health and aging. While, FRAX, relying on self-administered questionnaires, may not be the most efficient tool for population-based screening programs, given its low and differential participation rate, findings indicated that the program has proven effective if sufficient number of moderate-high risk individuals accept DXA. Consequently, further research aimed at enhancing fracture risk prediction and screening uptake is warranted.

Contributors

KHR is the chief investigator for the 10-year follow-up of the ROSE program and has coordinated the trial. TGP did the analysis-plan and statistical analyses and wrote the first draft with input from KHR and BA. Both TGP and KHR have directly accessed and verified the underlying data in the manuscript. KHR, BA, MH, MJR, TH, JG, MB, and APH developed the trial design and contributed to the management or administration of the trial. All authors contributed to the analysis-plan and the writing of the final manuscript. All authors had full access to all the ROSE data in the study and were ultimately responsible for deciding to submit it for publication.

Data sharing statement

The ROSE data and register data for the ROSE program are stored on a secure server at Statistic Denmark. Due to Danish legislation, microdata kept on the server cannot be shared for disclosure. Aggregated data (results) and do-files can be extracted and shared upon request by emailing the corresponding author. The study protocol has been published in Rubin et al. et al. The risk-stratified osteoporosis strategy evaluation study (ROSE): a randomized prospective population-based study. Design and baseline characteristics. Calcif Tissue Int. 2015; 96 (2):167–79.

Declaration of interests

BA has received institutional research grants from UCB, Kyowa-Kirin and Pharmacosmos, personal consulting fees from UCB and Kyowa-Kirin, and speakers fees from Gedeon-Richter. APH has received Lecture honoraria from UCB, AMGEN, and Gideon Richter, Travel Grants from UCB, and grant to participate on a Data Safety Monitoring Board/ Advisory Board from UCB and Gideon Richter. KEÅ has received lectures without fees from Amgen, UCB, and honoraria from Astellas Pharma. MKJ has received personal honoraria from Amgen, UCB, Abbvie, Besin Healthcare, and Sanofi and personal support for attending meetings/travel from UCB.

Acknowledgements

The ROSE study was jointly funded by INTERREG (4A JNR 08/4177), the Region of Southern Denmark (JNR 08/8133), and Odense University Hospital (JNR 11/5761).

We want to acknowledge biostatistician Anna Mejldal, who contributed with input to the analysis plan for the 10-year follow-up of the ROSE program, and Frederik Lykke Petersen, who helped carry out data management for the study, both affiliated at OPEN, Odense University Hospital, Denmark.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102584.

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