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Validation and robustness of the Fracture Risk Evaluation Model (FREM): A register-based cohort study

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Background

The Fracture Risk Evaluation Model (FREM) was developed for automated case finding of high-risk individuals of major osteoporotic fractures (MOF) or hip fracture (Rubin et al 2018) using a nationwide population- and register-based cohort aged 45 years or above the 1st of January 2013.

The model identified 38 and 43 risk factors for MOF for women and men, respectively, and 32 risk factors for hip fracture for both women and men. The model assessed a one year risk of fracture with a 15 years look-back period.

Objective

The aim of this study was to validate and test robustness of the internal validity of the FREM model.

Results

As of January 1, 2014, the total population of individuals age 45 years or above living in Denmark was 2,548,159 (1,317,327 women and 1,230,832 men). Median age was approximately 61 years, slightly higher for women. Men had a lower risk of fractures ($p < 0.001$) compared to women. The risk increased in both genders with age. No differences were found in number of comorbidities between genders or outcome years.

The AUC decreased slightly from the original FREM 2013 to year 2018 and was generally slightly lower for five years than for 15 years look-back exposure period. The PPV and NPV remained stable over time. Table 1 shows the C-statistics, PPV, and NPV for women. Similar results for men (results not shown).

Methods

Using the Danish national health registers we validated the FREM model in five one-year cohorts (2014-2018) with a 15-years look back period stratified by gender. To test robustness, we re-ran analyses to evaluate the model with 1) a 5-year look-back period and 2) 5-year fracture risks. Within each period, we determined an individual risk score and determine the occurrence of fractures during the outcome period. We estimated Receiver Operating Curves (ROC) with Area under the Curve (AUC, C-statistics) as well as positive (PPV) and negative predictive values (NPV) with 95% confidence intervals.

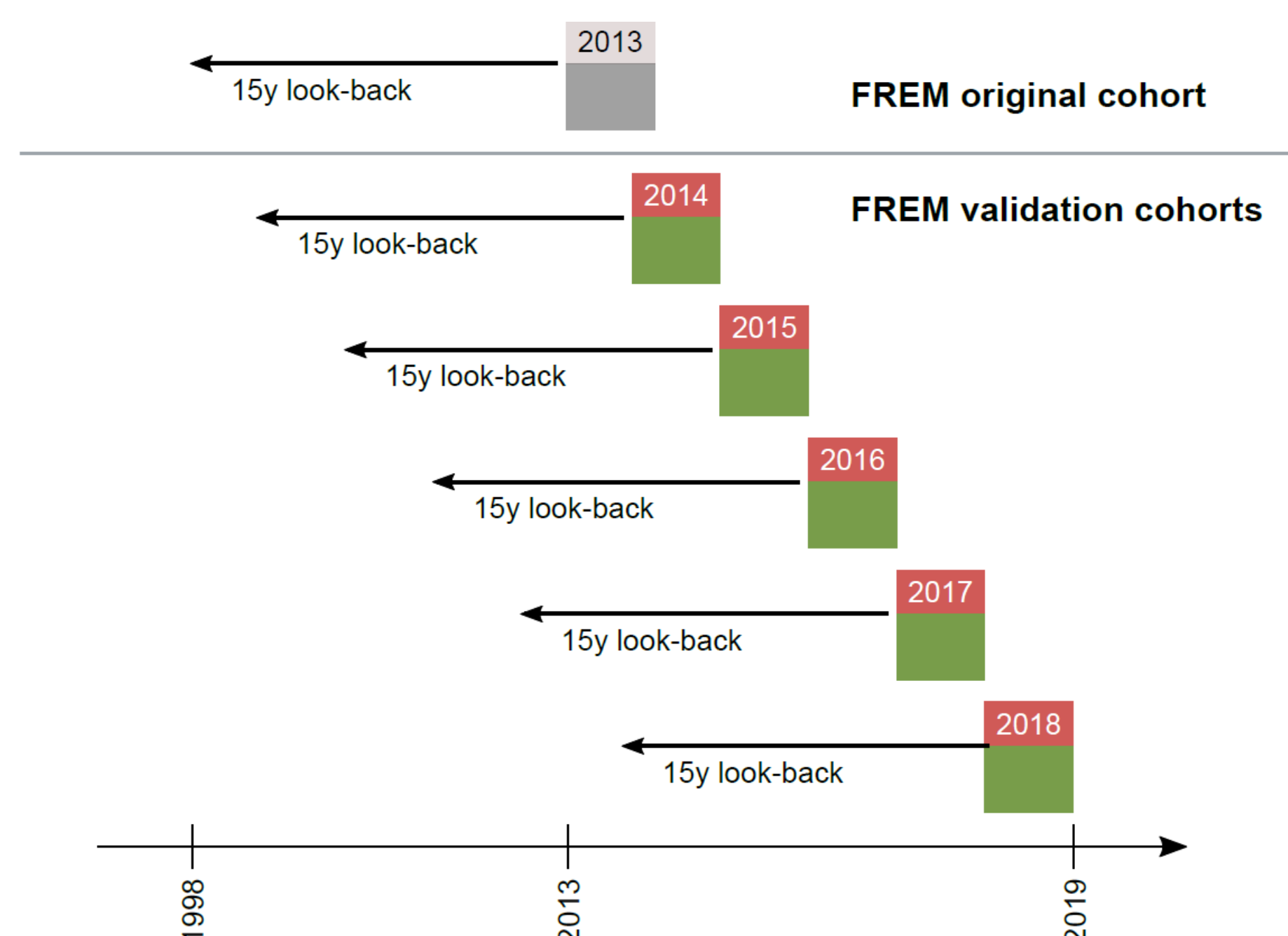


Figure 1. Time frame for validating the Fracture Risk Evaluation Model in five one-year cohorts (2014-2018)

Table 1. Performance and predictive capabilities of FREM in **women** by outcome year(s) with 15 years look-back period

	Year 2013 *	Year 2014	Year 2015	Year 2016	Year 2017	Year 2018	Year 2014-2018
	N= 647,103	N=1,317,327	N=1,328,972	N=1,340,359	N=1,352,654	N=1,365,537	N=1,317,327
Major osteoporotic fractures (with 15 years look-back period)							
C-statistic	0.75	0.76	0.75	0.75	0.75	0.74	0.72
(95% CI)	(0.74-0.80)	(0.75-0.76)	(0.75-0.75)	(0.75-0.75)	(0.74-0.75)	(0.74-0.75)	(0.72;0.72)
PPV (95% CI)	4.0	4.3 (4.2-4.4)	4.3 (4.2-4.3)	4.1 (4.0-4.2)	4.0 (3.9-4.1)	3.9 (3.8-4.0)	22.0 (21.0-23.1)
NPV (95% CI)	99.2	99.2 (99.1-99.2)	99.1 (99.1-99.2)	99.1 (99.1-99.2)	99.1 (99.1-99.1)	99.1 (99.1-99.1)	93.4 (93.3-93.4)
Major osteoporotic fractures: (with 5 years look-back period)							
C-statistic	Na	0.75	0.74	0.74	0.74	0.73	0.71
(95% CI)	Na	(0.75-0.75)	(0.74-0.75)	(0.74-0.74)	(0.73-0.74)	(0.73-0.74)	(0.71;0.72)
PPV (95% CI)	Na	4.6 (4.5-4.7)	4.6 (4.5-4.7)	4.5 (4.4-4.5)	4.3 (4.2-4.4)	4.2 (4.1-4.3)	23.3 (21.1-25.6)
NPV (95% CI)	Na	99.1 (99.1-99.1)	99.0 (99.0-99.1)	99.0 (99.0-99.1)	99.0 (99.0-99.1)	99.0 (99.0-99.0)	93.3 (93.3-93.4)

*Data from the validation sample of the previous published FREM development study (Rubin 2018)

Conflict of interest: The authors report no conflict of interest.



Contact

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Conclusion

The performance of FREM was comparable to previous findings. Results were virtually the same with only a five-year look-back exposure period, and the model predicted five-years risk of fractures almost as well as the one-year predictive risk.