# ESTIMATION OF RISK IN THE FIELD OF OSTEOPOROSIS

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin

vid Göteborg universitet kommer att offentligen att försvaras i hörsal Inge Schiöler,

Academicum, Medicinaregatan 11, Göteborg fredagen den 6 maj 2011, kl. 13.00.

av

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Avhandlingen baseras på följande delarbeten:

**I** **A Meta-Analysis of Prior Glucocorticoid Use and Fracture Risk.**

Kanis JA, Johansson H, Odén A, Johnell O, De Laet C, Melton LJ, Tenenhouse A, Reeve J, Silman AJ, Pols H, Eisman JA, McCloskey EV, Mellström D.

*J Bone Miner Res 2004; 19 (6): 893-99.*

**II** **The use of clinical risk factors enhance the performance of BMD in the prediction of hip and osteoporotic fractures in men and women.**

Kanis JA, Odén A, Johnell O, Johansson H, De Laet C, Brown J, Burckhardt P, Cooper C, Christiansen C, Cummings S, Eisman JA, Fujiwara S, Glüer C, Goltzman D, Hand D, Krieg MA, La Croix A, McCloskey EV, Mellström D, Melton LJ, Pols H, Reeve J, Sanders K, Schott AM, Silman A, Torgerson D, van Staa K, Watts NB, Yoshimura N.

*Osteoporosis International. 2007; 18(8): 1033-1046.*

**III** **Low bone mineral density is associated with increased mortality in elderly men: MrOS Sweden.**

Johansson H, Odén A, Kanis J, McCloskey EV, Lorentzon M, Ljunggren Ö, Karlsson MK, Orwoll E, Tivesten Å, Ohlsson C, Mellström D

*Osteoporosis International 2010 (E-pub ahead of print)*

**IV** **Low serum vitamin D is associated with increased mortality in elderly men. MrOS Sweden**

Johansson H, Odén A, Kanis J, McCloskey E, Lorentzon M, Ljunggren Ö, Karlsson MK, Tivesten Å, Barrett-Connor E, Ohlsson C, Mellström D

*Submitted*

**V** **High serum adiponectin predicts incident fractures in elderly men. Mr OS Sweden.**

Johansson H, Odén A, Lerner U, Jutberger H, Lorentzon M, Barrett-Connor E, Karlsson M, Ljunggren Ö, Smith U, McCloskey E, Kanis J, Ohlsson C, Mellström D

*In manuscript*

Göteborg 2011

**UNIVERSITY OF GOTHENBURG**

# ESTIMATION OF RISK IN THE FIELD OF OSTEOPOROSIS

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## ABSTRACT

**Introduction**: Osteoporosis has been recognised as an established and well-defined disease that affects more than 75 million people in the United States, Europe and Japan. Osteoporosis has been operationally defined by the WHO on the basis of bone mineral density (BMD) assessment. Although risk factors for fracture are well-known and thoroughly investigated, osteoporosis is an under-diagnosed and under-treated disease in women, and even more so in men.

**Objective**: The general objective of this work is in the context of the development an assessment tool (FRAX) for the prediction of fracture in men and women with the use of clinical risk factors for fracture with and without the use of femoral neck BMD. The rationale arises from the observation that factors other than BMD contribute towards fracture risk and that estimates of probability permit the integration of multiple clinical risk factors (CRFs) including the competing risk of death. The material presented in this thesis aims to illustrate several components of this work. The first is the identification of a clinical risk factor (exposure to glucocorticoids) as a potential candidate for its inclusion into the FRAX algorithm. A second aim was to determine the increase in operating characteristics of combining clinical risk factors with and without the inclusion of BMD. A novel feature of the FRAX models is that they integrate the fracture and death hazards in the determination of fracture probabilities. Several clinical risk factors affect the death hazard as well as the fracture hazard, so that a third aim was to explore the effect of a well established CRF (BMD) and a potential CRF (serum 25-hydroxyvitamin D) on the risk of death. A final aim was to determine the potential of a new candidate risk variable (serum adiponectin) for fracture.

**Methods:** To create the risk assessment tool baseline and follow-up data is used from eleven international prospective population-based cohorts comprising 15 259 men and 44 902 women with 5 563 fractures of any kind and 978 hip fractures. Cohorts were followed for a total of over 250 000 person years. Primary data from the cohorts is used so that important interactions could be determined. In addition a Swedish cohort of 3 014 elderly men (MrOS) is used, drawn from the general population.

**Results:** The risk factors incorporated in the assessment tool comprised body mass index (as a continuous variable), a prior history of fracture, a parental history of hip fracture, use of oral glucocorticoids, rheumatoid arthritis, current smoking and alcohol intake >2 units daily. Their inclusion was based on their international validity and independent contribution to fracture risk. Four models were then constructed to compute fracture probabilities in nine of the cohorts. These comprised the probability of hip fracture, with and without femoral neck BMD, and the probability of other osteoporotic fractures, with and without BMD. For each model fracture and death hazards functions were computed and used to compute 10-year fracture probabilities (FRAX). The model could be calibrated to any country where the epidemiology of fracture and death is known. In the publications included in this thesis, exposure to glucocorticoids is shown to be a significant risk factor for fracture, providing the rational for the inclusion of this CRF in the FRAX algorithms. We also show that the incorporation of CRFs improves the operating characteristics of fracture risk assessment over and above that provided by BMD alone. In elderly men in the Swedish MrOS cohort, it is shown that low BMD is associated with increased mortality in a non-linear pattern (overall gradient of risk (GR) 1.27; 95% CI 1.14-1.42, multivariable adjusted), that low vitamin D is associated with increased mortality (overall GR; 1.15; 95% CI 1.03-1.29, multivariable adjusted) and that the association wanes with time. It is also shown that high adiponectin is associated with higher fracture risk in elderly men (overall GR; 1.32; 95% CI 1.15-1.52, multivariable adjusted).

**Conclusion**: Components of the work in this thesis have contributed to the creation of FRAX, a fracture risk assessment tool, that has been recommended by WHO and is widely used in clinical practice to identify patients suitable for pharmacological intervention. In elderly men it is showed that low BMD and low vitamin D are risk factors for death and high adiponectin is a risk factor for fracture. The biostatistical contribution to these associations is the identification of non-linearity of the associations and their dependence on time since baseline assessment.

**Keywords**: osteoporosis, fracture, bone mineral density, clinical risk factors, FRAX, Poisson model, 10 year probability, mortality, vitamin D, adiponectin

ISBN 978-91-628-8275-4