SCREENING FOR LOW BONE MINERAL DENSITY IN PATIENTS WITH RESPIRATORY DISEASE

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Abstract

Patients with respiratory disease have decreased mean bone mineral density (BMD) and thereby increased risk of fractures compared to people without respiratory disease. We developed a clinical screening tool to identify patients *unlikely* to have low BMD who do *not* require bone densitometry, and estimated number needed to screen (NNS) and number needed to treat (NNT) to prevent one hip fracture in this patient group.

Methods: A cross-sectional convenience sample (N=239) of patients from public hospitals and general practice with respiratory disease had their BMD assessed using dual-energy X-ray absorptiometry (DXA). Risk factors for low BMD (*Z*-score <-1.5 at lumbar spine, neck of femur or total femur) were analysed using multiple stepwise logistic regression. NNS to prevent one hip fracture using daily alendronate (10mg) at 1 and 10 years were developed using equations in Kanis, 2000,[1] and by extending the results to ten years using a Markov simulation.

Results: Participants with respiratory disease and ALL of: BMI >20; smoked <80 pack years; not currently using warfarin; FEV_1 ≥60% predicted were NOT recommended for DXA, thereby eliminating 35% of participants. At selected sensitivity of 86%, this tool has specificity of 41%, positive predictive value 27% and negative predictive value of 92%; area under the ROC curve was 0.7. Number needed to screen for 65 year old women with respiratory disease and low BMD (*Z*<-1.5) is ~1800 for treating with alendronate for 1 year and 165 for 10 years of treatment. Using the screening tool to reduce the number of patients screened by eliminating the 35% not requiring densitometry may reduce NNS for 1 year of treatment by 35% to ~1,400 for 65 year old women with COPD and BMD of *Z*<-1.5, and NNT to ~440 to prevent one hip fracture.

Conclusions: Our pre-screening tool has high negative predictive value, and therefore may assist clinicians to identify those who would benefit most from densitometry. NNS estimates for 65 year old women are reasonable. Using this screening tool together with NNS may enable the development of a cost-effective screening program for low BMD in respiratory patients.

Declaration

This work contains no material that has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to the copy of my thesis, when deposited in the University Library, being available for loan and photocopying

Signed:

Laura Louise Laslett (nee Smith)

October, 2003

List of abbreviations

ABONE	Age, Body Size, No Estrogen (ABONE)
BMD	bone mineral density
BMI	body mass index = $\frac{\text{weight (in kilograms)}}{\text{height (in metres)}^2}$
COPD	chronic obstructive airways disease
CS	corticosteroid
CT	computed tomography
DPA	dual photon absorptiometry
DXA	dual emission X-ray absorptiometry
eg.	for example
FEV_1	forced expiratory volume in one second
FH	Family history of osteoporosis
g/cm^2	grams per square centimetre
GI	Gastro-intestinal
HRT	hormone replacement therapy
ICS	inhaled corticosteroids
kg	kilogram (unit of weight)
LS	lumbar spine
LYG	life years gained
m	metres
mg	milligram (unit of weight)
mrem	millirem (unit of radiation)
n.s.	not (statistically) significant
n/a	not applicable
NIH	National Institute of Health (United States of America)
NNS	number needed to screen
NNT	number needed to treat
NOF	Neck of femur
OCS	Oral corticosteroids
PBS	Pharmaceutical Benefits Scheme (Australia)
QALY's	quality adjusted life years' gained
QCT	quantitative computed tomography
RA	radiographic absorptiometry
RCT	randomised controlled trial
ROC curve	receiver operator characteristic curve
SCORE	Simple Calculated Osteoporosis Risk Estimation
SD	standard deviation
sig	(statistically) significant
SPA	single photon absorptiometry
SXA	single x-ray absorptiometry
T-score	Bone density - number of standard deviations from the young adult mean for gender
UK	United Kingdom
US	United States of America
WHO	World Health Organisation
Z-score	Bone density - number of standard deviations from the age and gender matched mean

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"I can do everything through him who gives me strength" (Philippians 4:13).

Chapter 1 – Introduction

1.1 What is osteoporosis?

Osteoporosis is a "progressive, chronic disease which is characterised by low bone mass and a microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk".[2] Osteoporosis constitutes a major public health problem through its association with fractures, costing Australian taxpayers $7.4 billion per annum, and over 25,000 healthy lives lost in the financial year 2000-01.[3]

People with chronic lung diseases such as chronic obstructive pulmonary disease (COPD) and asthma are at high risk of osteoporosis, with on average 10% lower bone mineral density (BMD) than controls[4] with the largest deficits seen in patients with most severe disease. The rates of actual bone fracture in people with COPD are also high, with estimates of 11-56% in oral corticosteroid-dependent asthmatics, compared with 0-8% in people taking intermittent oral corticosteroids or inhaled corticosteroids only.[5,6]

High quality tests are available to determine bone mineral density and hence diagnose low BMD. Effective treatments exist, although the efficacy and cost-effectiveness of full screening and treatment programs are yet to be evaluated in people with respiratory disease.

1.2 Key questions for this thesis

In order to decide whether screening and treatment of low bone density in people with airways disease is likely to be efficacious and cost effective, the following questions must be considered.[7,8]

- Does low bone density cause sufficient mortality and morbidity to warrant routine screening?

The magnitude of the problem of low bone density in the general population and in people with COPD or airways disease need to be considered, as does why patients with COPD or airways disease are at high risk of having or developing low bone density than the general population.

- Is early treatment for low bone density during the asymptomatic (pre-fracture) phase of the condition effective in preventing or reducing morbidity and mortality?

- Is the screening test reasonably inexpensive, safe and acceptable to patients?
- Does the screening test have adequate predictive value?

If screening and treatment appear efficacious, then how can combinations of clinical risk factors be used to identify the patients at highest risk of developing low bone mineral density?

1.3 Project aims and hypotheses

Based on the above considerations, this thesis will investigate the following aims by original research:

1.3.1 Aim 1: To identify risk factors for low bone density

"To investigate whether suggested risk factors predict low bone density in people with asthma/airways disease by studying a large cohort of "at risk" subjects."

1.3.2 Aim 2 - Developing number needed to screen and number needed to treat estimates in the general population and subgroups with COPD

To determine the number needed to screen in the general population and a subgroup of the general population who have COPD by screening with DXA, to identify a high-risk population - and in that population, the number needed to treat for treatment with daily alendronate for one and ten years to prevent one hip fracture.

These lead to hypotheses 1 and 2:

1.4 Hypothesis 1

That patients with "low" (Z<-1.5) or "not low" (Z>-1.5) BMD (matched for age and gender) at either total femur or neck of femur or lumbar spine differ significantly for one or more risk factors for low BMD using an χ^2 test for categorical variables, or logistic regression for continuous variables.

1.5 Hypothesis 2

That the number needed to treat and number needed to screen will be able to be estimated for treating patients in the general population and the COPD population with daily alendronate for 1 or 10 years by the use of economic models generated using Microsoft Excel.

Chapter 2- Literature review: Is screening for and treating low bone density effective in people with airways disease?

2.1 Does low bone density cause sufficient mortality and morbidity to warrant routine screening?

2.1.1 Magnitude of the problem in the general population

Osteoporosis presents clinically as bone fractures. Traditionally osteoporosis is linked to the proximal femur (hip), vertebrae (spine), and distal forearm (wrist), although because bone is lost throughout the skeleton, fractures can occur at other sites, such as the ribs.[9]

Following a peak in early adulthood, bone density in absolute units (g/cm^2) declines with advancing age. Men have a higher peak bone mass than women, and thus have higher bone density than women in middle and old age.[10,11]

The most widely used definition of low bone density is the (World Health Organisation (WHO) definition.[12] Medicare uses additional definitions for determining rebates after bone densitometry using dual emission X-ray absorptiometry (DXA) (See Table 1).[13]

Table 1 - Definitions of "osteoporosis" currently in use in Australia based on low BMD

Name	Reference	Matched for	Cutoff
World Health Organisation (WHO) definition of low BMD[12]	Mean BMD of young adults (25 – 29 years)	Gender Site	"Osteopenia" T<-1.0 "Osteoporosis" T<-2.5
Medicare definitions of "low BMD" based on actual BMD[13]	As above	As above	*T*<-2.5
	Mean BMD of the general population	Gender, age, race, site, sometimes weight	*Z*<-1.5

Medicare rebates can also be obtained for densitometry (using DXA) if patients have one or more fractures occurring after "minimal trauma" (males or females), where DXA will be confirming a presumptive diagnosis of low BMD, or for the diagnosis or monitoring of prolonged glucocorticoid therapy, conditions associated with excess glucocorticoid secretion, male hypogonadism, or female hypogonadism lasting >6 months after age 45.[13] These conditions essentially constitute clinical definitions for low BMD. However, low BMD as measured by densitometry will be the focus of this thesis because it is more objective.

The WHO definition of low BMD identifies age-related bone loss relative to the young adult mean (aged 20-29 years) in standard deviation units, and these measurements are referred to as *T*-scores. Consequently, the prevalence of men and women with low bone density according to the World Health Organisation (WHO) increases with advancing age. An estimated 2-17% of women and 2-7% of men in European/US

reference populations aged 50-79 have low bone density at the total femur using this definition (See Table 2).[10]

Table 2 - Prevalence of low BMD (*T*<-2.5) in men and women aged 50-79

Age	Women	Men
50-59	2.70%	2.30%
60-69	7.40%	3.80%
70-79	17.10%	7.10%

As indicated in Table 1, there are two definitions of low BMD (based on actual BMD) for Medicare rebate purposes. One is equivalent to the WHO definition of low BMD (*T*<-2.5). The other is unique to Medicare, and this definition of low BMD identifies causes of reduced bone density beyond age, such as that related to medication or illnesses. The proportion of a population with low BMD at any particular site according to this definition (*Z*<-1.5) is always the same for each gender regardless of age because *Z*-scores are standardised for age and gender (6.68%).

2.1.2 Relationship between BMD and fracture risk

BMD is a good predictor of fracture risk,[14] with each standard deviation decrease in hip BMD conferring a 2.6x increase in age-adjusted hip fracture risk,[15] and a two standard deviation reduction in vertebral BMD conferring a 4-6-fold increase in vertebral fracture risk.

There are other predictors of fracture risk that are independent of BMD. These include age (as a surrogate for bone quality, medical illness, and propensity to fall)[16] [17] pre-existing fractures,[18] corticosteroid use,[19] hip geometry eg hip axis length,[20] and bone turnover.[21] In addition, quantitative ultrasound (QUS), which is often used as a radiation-free, more accessible alternative to BMD assessment is also a strong predictor of fractures,[22] despite being only modestly correlated with BMD (r=0.4 – 0.7), raising suggestions that QUS may measure other aspects of fracture risk that BMD is unable to assess, such as bone quality. Therefore, despite the evidence that BMD as assessed by DXA is not the only predictor of fracture risk, and the fact that other risk factors can add extra information to fracture prediction, BMD is still a good measure of fracture - similar to or better than serum cholesterol concentrations for cardio-vascular disease,[17] or of blood pressure to predict stroke.[23]

Cross-sectional studies show linear changes in BMD,[24-33] whereas longitudinal studies indicate that the rate of bone loss is not strictly linear, but increases with

advancing age,[25,34-37] with rates of change of 0.51-0.96% per year at the neck of femur in women[34,35,37] and 0.4-0.82% per year in men.[34,37] Similar patterns were also reported at the calcaenus,[35] but not the spine,[37] probably due to coexistent spinal degenerative disease.

Possible reasons explaining the apparent difference between findings in cross-sectional and longitudinal studies include limitations in sample size,[38] cohort effects such as increase in heights in younger generations compared to older people, which would overestimate rates of bone loss with aging in cross sectional studies,[39] and low BMD is associated with increased mortality rates in older women, with sicker women under-represented in cross-sectional studies.[40] The DXA machine used in the research described in this thesis uses reference populations from Europe and the UK from cross-sectional data.[34,34,41-45] The use of cross-sectional data may slightly over-estimate age-adjusted mean BMD in the oldest age groups (≥70 years).

2.1.3 A closer look at fractures

Hip fractures cause the most morbidity and mortality, with hip fracture patients 30% more likely to be institutionalised and 18% more likely to have died one year post-fracture compared to community based controls.[46] Hip fractures also result in loss of independence, with 31% of previously ambulatory patients unable to walk one year after the hip fracture.[46] Older patients were more likely to have a poorer outcome eg non-ambulation or death.[47] Some morbidity was associated with fractures of the spine or distal forearm eg higher rates of depression and poorer quality of life,[48] but patients who sustained these fractures were no more likely to have died than patients without fractures.[48]

Most fractures (70-80%) occur in women,[49] due to lower peak bone mass and longer lifespan in women compared to men.[50] The numbers of actual fractures and fracture risk in men and women in the general population and in the COPD population will be discussed in order to decide whether fractures are of public health significance.

2.1.4 Australian estimates of fracture incidence

Community fracture incidence has been estimated in three large Australian studies.[51,52,53] As fracture rates increase with advancing age,[10,11] and the Australian population ages (median age 34 in 1996 compare with 32 years in 1991[54]) the incidence of many (if not all) fractures are likely to increase as there are more people than ever before in the older age groups most susceptible to hip fractures.

Estimates from the Geelong Osteoporosis Study group suggest that over the period 1996 - 2006, total number of fractures may increase by 25%. Hip fractures may increase by 36% over 1996-2006, and may double by 2026.[55]

Assuming these projections are correct, by 2006 31,000 Australians aged over 45 may experience a fracture per annum. If these figures are extrapolated to the entire Australian population,[54] then by 2006, the number of hip fractures may have risen so greatly that over 14,000 people aged over 45 will experience a hip fracture per annum, and by 2051 this may increase to over 42,000 Australians per annum. With a corresponding yearly post-fracture mortality rate of 27%,[47] by 2026 an estimated 11,400 Australians over 45 may die each year after sustaining a hip fracture.

2.1.5 Magnitude of the problem of low bone density in people with COPD or airways disease

Chronic lung disease is common in Australia, with the prevalence of moderate to severe chronic lung disease in South Australia estimated to be 5% in people aged 45-54, 6% in people aged 55-64, and 11% in people aged 65 and over.[56]

A number of small studies of patients with COPD have found high numbers of bone fractures in addition to low BMD. The prevalence of rib or vertebral fractures in patients with asthma or COPD taking daily oral corticosteroids is 42% - 50%,[5,6] and the prevalence of vertebral fractures alone is estimated at 34%,[6] compared to none (0%) in patients with asthma or COPD patients taking intermittent oral corticosteroids,[5] although people taking inhaled corticosteroids may have been X-rayed less frequently than those taking OCS as they would have had less severe respiratory disease. Despite the small numbers of patients included (and likely selection bias), the large number of fractures observed highlights a clinically important problem, particularly in subjects with advanced disease.

A review article which summarised bone density reduction in nine cross-sectional studies in patients with asthma or airways disease.[4] The review concluded that patients with asthma or COPD are a group at high risk of developing low bone density. An average 10% BMD reduction compared to controls was found, with greatest deficits in patients with more severe disease, although all the trials were in small numbers of patients.[4]

A 10% average decrease in BMD for patients with airways disease suggested by Smith *et al.*[4] equates to approximately one standard deviation, with an associated 2.6 times increase in hip fracture risk.[57]

Estimates for fracture burden in the Australian COPD population can be made by using the fracture rate for the general population, multiplying this by the prevalence of COPD in each age group, multiplying by 2.6 (increase in fracture risk due to COPD status,[4]) then multiplying by literature estimates of future fracture burden.[55]

Assuming these estimates are accurate, 7.5% of the Australian population with COPD may contribute around 7,900 fractures per annum in 1996-2006, including around 3,600 hip fractures. By 2026 this may increase to 4,300 hip fractures and 11,500 per annum for the Australian COPD population by 2051. Mortality rates at one year after the hip fracture are 18% higher than expected (in non-COPD subjects),[47] therefore approximate numbers of deaths in the COPD population

attributable to the hip fracture in the year following the fracture are 650 per annum 1996-2006, 775 per annum by 2026, 2050 per annum by 2051.[47]

2.1.6 Conclusion – Does the condition cause sufficient mortality and morbidity in people with airways disease to warrant routine screening?

Large numbers of Australians sustain fractures (particularly hip fractures) and the associated poor outcomes have significant public health implications. This magnitude of the problem will increase dramatically over time as Australia's population ages, and there are more people in the age groups with high fracture incidence. People with chronic airways limitations such as asthma, emphysema and COPD have high levels of actual bone fracture, low BMD, and associated high risk of developing osteoporotic fractures. Consequently, the morbidity and mortality associated with osteoporotic fractures for this group is particularly large. The projected number of fractures in the next 30-50 years is sufficiently large to consider a case for screening for low BMD in patients with moderate to severe airways disease, with a view to lowering fracture rates in this group of people with anti-osteoporosis treatments.

2.1.7 Why patients with COPD or airways disease are at increased risk of developing low bone density

The use of clinical risk factors has been suggested to aid in identifying people who have low BMD or are at high risk of developing low BMD. Risk factors are indicators of an individual's likelihood of developing low BMD, and can therefore be used as part of a screening strategy - provided they predict low BMD with sufficient precision to enable bone mass measurements to be avoided.[58]

Risk factors that may predispose an individual to develop low BMD or be associated with low BMD will be discussed in women and men in the general population or with respiratory disease.

Articles describing research on the effect of lifestyle or anthropomorphic factors on bone density in women and men in the general population or in people with respiratory disease were sought from the literature using the following keywords:

("risk-factors" AND "bone-density" AND "questionnaire*") or ("risk-factors" AND "questionnaire*" AND "explode "Osteoporosis"/ all subheadings"). Hand searching of the reference lists of identified studies was also conducted to yield additional relevant articles not identified using the above method.

The search found studies that tested whether an individual risk factor was associated with low bone density (univariate analysis), and also studies that tested whether a number of risk factors considered together were associated with low bone density (multivariate analysis). These analyses have different purposes – univariate analyses show that the individual risk factor is or is not associated with low BMD. Multivariate analyses show the contribution of each risk factor to predicting low BMD, enabling us to see which risk factors best predict low BMD when a number of risk factors are considered at once. Multivariate analyses are preferable to univariate analyses because they simulate reality more effectively as risk factors do not operate in isolation.

A summary of the studies referred to in this section is tabulated on Table 74, Table 75, and Table 76 (Appendix 1, pages 192 - 194), including numbers of patients and sampling frame. Risk factors applicable to the general population and those applicable specifically to patients with asthma or COPD will be discussed. Both categories of risk factors contribute to low BMD and increased fracture risk in this patient group.

2.1.7.1 Risk factors applicable to the general population

The following risk factors will be discussed in this section: age, body size (body mass index (BMI), weight, and height), previous fractures, low levels of physical activity or immobilisation, cigarette smoking, family history of osteoporosis, and calcium intake.

2.1.7.1.1 Age

Data from cross-sectional surveys of reference populations show that bone density (as measured in g/cm^2) declines with advancing age. [10,11] The bone density of women peaks in early adulthood, declining slightly until menopause, then declining faster after menopause, with the rate of loss increasing into old age. The bone density of men peaks in early adulthood then decreases in a similar manner to women, except without any change in the rate of bone loss around middle age. Advancing age is also associated with low bone density in most sub-groups in many[59-66] but not all[67,64,66] cross-sectional studies tabulated in Table 3. No association was found between age and BMD in the study by Reid & Heap, 1990[67] who used *Z*-scores to measure BMD, (which are standardised for age, gender, and weight), and therefore no relationship between age and BMD in this study would be expected. Whilst age is independently related to low BMD,[16,17,19] it may also be a surrogate marker for other age-related factors including decreased physical activity, and increasing severity of respiratory disease, which may also affect BMD. Advancing age may also accelerate differences in BMD between smokers and non-smokers.[68]

Table 3 – Association of age and bone density

Study name	Site	Statistical technique	Regression coefficient	p value
Bauer, 1993[59]	Radius	% change in BMD	-3%	<0.05 at multi-variate level
Elliot, 1993[60]	Women LS NOF Men LS NOF	Multiple linear regression	-0.44 -0.54 -0.03 -0.39	<0.001 <0.001 n.s. <0.001
Ribot, 1992[61]	LS	Multiple logistic regression	1.264	<0.001
Stevenson, 1989[62]	NOF	Correlation coefficient	-0.24	<0.005
Ip, 1994[63]	Ward's triangle	Spearman rank correlation	n/a	<0.03
Laatikainen, 1999[64]	NOF LS	Multiple linear regression	-0.06 -0.3	n.s. <0.01
Wong, 2000[65]	LS (men & women)	Univariate regression coefficient	0.016	0.03
Slemenda, 1990[66]	LS NOF Radius	Univariate correlation coefficients	-0.09 0.06 -0.2	n.s. n.s. 0.05<p<0.10
Reid & Heap, 1990[67]	LS t-test (Z-scores)	n/a	0.13 (n.s.)	

LS = lumbar spine, NOF = neck of femur, n.s. = not statistically significant

Conclusion

Advancing age is associated with decreasing bone density in many but not all cross-sectional studies listed in Table 3, and the association appears strong.

2.1.7.1.2 Body size

Small body size is associated with low BMD, as higher weight for a given height increases the skeletal loading on the body, encouraging the body to make bones thicker and stronger to support extra weight, and also affects the rate of change of BMD.[37] Investigations of factors relating to body size (BMI, height, and weight) in cross-sectional studies are investigated in Table 4, Table 5 and Table 6. The studies described in Table 4 were mostly asthmatics,[63,64,65,69,70] with one study including patients with COPD[71] Thompson *et al.*[70] included only a minority of patients with respiratory disease (See Table 71 for more detailed information on the sampling frame of these studies). If body size parameters demonstrate significant associations with low BMD, this is advantageous because weight and height are routinely collected at many hospital outpatient clinics and general practices.

2.1.7.1.2.1 Body mass index (BMI)

Table 4 – Association of body mass index (BMI) and bone density *

Study name	Site	Units	Regression coefficient	P value
Ip, 1994[63]	LS Trochanter	Univariate correlation	- -	0.02 <0.02
Laatikainen, 1999[64]	LS NOF	Univariate correlation	0.209 0.484	<0.05 <0.001
Wong, 2000[65]	LS	Univariate regression coefficient	r=0.008	0.001
Sivri, 2001[69]	LS Proximal femur	Correlation coefficient	Positive (not stated)	≤0.05 <0.05
Iqbal, 1999[71]	NOF LS	Correlation coefficient	r=0.346 r=0.202	<0.001 <0.01
Thompson, 1997[70]	NOF LS	Multiple linear regression	R^2=0.13 R^2=0.07	<0.005 0.07

LS = lumbar spine, NOF = neck of femur
* Only 12% of the patients in the study by Thompson, 1997[70] had respiratory disease (asthma). The remaining patients were postmenopausal women who required daily oral corticosteroids for non-respiratory medical conditions.

BMI was significantly associated with low BMD in these patients (see Table 4), although only one of these six studies used BMI in a multivariate model (Thompson *et al.*[70])

BMI was significantly associated with low BMD in these respiratory patients (see Table 4), although only one of these six studies used BMI in a multivariate model (Thompson *et al.*[70]).

Some studies separated weight and height instead of combining them in BMI. These are presented in Table 5 and Table 6. Where both weight and BMI are included in a multivariate model, BMI is preferred,[65] as it gives additional information regarding build and body size.[64]

Conclusion

High body mass index is associated with high bone density at the lumbar spine, and femur (neck of femur, proximal femur and trochanter) in men and women with respiratory disease, and the association appears strong. Therefore, as BMI decreases, so does BMD.

2.1.7.1.2.2 Weight

Table 5 – Association of weight and bone density in men and women in the general population and with respiratory disease

Pre-menopausal women

Study name	Site	Units	Regression coefficient	P value
Stevenson, 1989[62]	LS NOF	Univariate correlation	0.18 0.04	n.s. n.s.
Wong, 2000[65]	LS (men and women)	Univariate regression coefficient	0.03	0.001
Slemenda, 1990[66]	LS NOF Radius	Multivariate regression coefficient	0.0043 0.0041 0.0022	Sig Sig Sig
Torgerson, 1995[72]	NOF	Stepwise multiple regression	0.0042	<0.0001

Postmenopausal women

Bauer, 1993[59]	Radius	% change in BMD	3.7%	<0.05 at univariate level
Ribot, 1992[61]	LS	Multiple Linear Regression Coefficient	-0.23	0.004
Stevenson, 1989[62]	LS NOF	Univariate correlation	0.24 0.22	<0.005 <0.005
Ballard, 1998[73]	LS and NOF	Univariate χ^2 analysis	N/a	0.0001

All ages (women)

Elliot, 1993[60]	LS NOF	Multiple Linear Regression Coefficient	0.37 0.28	<0.01 <0.001
Laatikainen, 1999[64]	LS NOF	Univariate correlation	0.209 0.484	<0.05 <0.001
Nguyen, 1994[74]	LS NOF	Multiple linear regression	0.06 0.05	<0.01 <0.01

Men

Elliot, 1993[60]	LS (men) LS (men)	Multiple Linear Regression Coefficient	0.48 0.39	<0.001 <0.001
Wong, 2000[65]	LS (men and women)	Univariate regression coefficient	0.03	0.001
Nguyen, 1994[74]	LS NOF	Multiple linear regression	0.05 -0.02	<0.01 <0.01

LS = lumbar spine, NOF = neck of femur
Only Laatikainen, 1999[64] and Wong, 2000[65] include subjects with respiratory disease, others include participants from the general population

Conclusion

Higher body weight is associated with higher bone density in men and women with and without respiratory disease, at the lumbar spine, neck of femur and radius, and the association appears strong. Therefore, as body weight decreases, so does BMD. Studies utilising BMI in multivariate models were mostly in patients with respiratory disease, whereas studies utilising weight in multivariate models were mostly in the general population. Therefore, it is difficult to decide whether weight or BMI is a better predictor of low BMD from these studies as they both appear equally good. However, BMI theoretically provides more information on body build and therefore may be better to include in multivariate models in practice.

2.1.7.1.2.3 Height

Table 6 – Association between height and bone density in men and women with respiratory disease and in the general population

Study name	Site	Units	Regression coefficient	P value
Pre-menopausal women				
Stevenson, 1989[62]	LS NOF	Univariate correlation	0.23 0.14	<0.025 n.s.
Slemenda, 1990[66]	LS NOF	Multivariate regression coefficient	0.17 0.04	<0.1 n.s.
Wong, 2000[65]	LS Men and women	Univariate regression coefficient	0.001	n.s.
Torgerson, 1995[72]	NOF	Stepwise multiple regression	0.0029	<0.001
Postmenopausal women				
Bauer, 1993[59]	Radius	Multivariate linear regression	1.7% change in BMD	<0.05 at univariate level
Ribot, 1992[61]	LS	Multiple Linear Regression Coefficient	-0.072	<0.001
Stevenson, 1989[62]	LS NOF	Univariate correlation	0.15 0.15	n.s. n.s.
Ballard, 1998[73]	LS and NOF	Univariate χ^2 analysis		n.s.
All ages (women)				
Elliot, 1993[60]	LS (women) NOF (women)	Multiple linear regression	0.03 0.07	n.s. n.s.
Nguyen, 1994[74]	LS NOF	Multiple linear regression	0.03 0.04	<0.01 <0.01
Men				
Elliot, 1993[60]	LS NOF	Multiple linear regression	0.12 -0.06	n.s. n.s.
Wong, 2000[65]	Men and women	Univariate regression coefficient	0.001	n.s.
Nguyen, 1994[74]	LS NOF	Multiple linear regression	0.04 0.02	<0.01 n.s.

LS = lumbar spine, NOF = neck of femur
Only Wong, 2000[65] included patients with respiratory disease

In multiple regression models which predict whether individuals will have low BMD, height and weight both make statistically significant contributions to the bone density prediction algorithms in pre-menopausal[66,72] and post-menopausal women,[59,61] but not in men.[60,74] Mixed results were found in studies that included participants with a wide range of ages.[60] A possible explanation for this may be that the relationship between BMD and height or weight is different at different ages, and by mixing

together a wide range of ages the effect may be diluted and is therefore no longer statistically significant. In univariate regression models, weight is statistically significant but not height[65,73,62] with the exception of the pre-menopausal group in Stevenson *et al.*[62] No studies included height alone. This mixed picture is consistent with studies investigating risk factors for hip fractures, with most finding that height does not predict risk of hip fractures in the larger studies,[75-77] although increased height does predict hip fracture in some studies.[78,79] Possible explanations for these discrepancies are that increased risk of hip fractures could be mediated through hip axis length, which is an independent predictor of hip fracture risk,[20] and is positively correlated with height. Another explanation is that people with the lowest BMD and highest fracture risk may be losing height as they age due to vertebral deformities, as one study found that height at age 25 was associated with hip fracture risk, but not height[76] – thereby diluting the association.

Conclusion

In the studies presented here, height does not appear to independently add extra information to enable bone density to be predicted over that contributed by weight when weight and height are entered into regression models separately.

2.1.7.1.3 Previous fractures

Fracture risk increases as BMD decreases, with every one SD decrease in age-standardised hip BMD conferring a 2.6-fold increase in risk for hip fractures,[57] and decreases of 2 standard deviations in spine BMD are associated with 4-6 fold increase in vertebral fracture risk.[80] Therefore, reduction in BMD increased the risk of sustaining a fracture. Patients with existing fractures should, therefore, have lower BMD than patients without existing farctures, and should also be at high risk of sustaining future fractures.

Luengo *et al.*[6] and Toogood *et al.*[81] investigated differences in BMD among asthmatics with and without vertebral fractures. Luengo *et al.*[6] also included a group of non-asthmatics with fractures (See Table 7). According to Luengo *et al.*[6] asthmatics with fractures have lower BMD than those without fractures.[6] This can be attributed to advancing age, because the effect disappears when standardised for age by the use of *Z*-scores,[81] although the standard deviation is large, making a difference between the two groups difficult to detect in such a small sample.

Table 7 – Lumbar BMD and fractures in asthmatics and non-asthmatics

	No fractures, asthma	Fractures, asthma	No asthma, fractures
Luengo, 1991[6]	(N=67)	(N=32)	(N=55)
Bone density (g/cm^2)	1.044±0.18	0.946±0.18 ($p<0.05$)	0.830±0.16 ($p<0.05$)
Age (years)	54±12†	58±9	63±11
Toogood, 1995[81]	(N=48)	(N=15)	-
Bone density (g/cm^2)	0.90±0.14	0.82±0.23 (p=0.10)	-
Z-score	-0.57±1.49	-1.01±1.72 (p=0.34)	-

"† "no fractures, asthma" group is younger than "no asthma, fractures" group

The data from Luengo *et al.*[6] has also been used to support a hypothesis that asthmatics fracture at a higher BMD than non-asthmatics, and that this phenomenon is corticosteroid-induced. This was also investigated by another research group, who found no evidence of such an effect.[82]

Table 8 – BMD in patients in the general population with and without bone fractures

	Colles' fracture Ooms, 1993[83]	Spine fracture Kröger, 1999[84]		Hip fracture Kröger, 1999[84]	
		Men	Women	Men	Women
Age (years)	80	57±11	64±9	66±10	76.4±10
N=	56 fracture, 328 non-fracture	50	284	12	39
Technique	% difference between fracture and non-fracture cases (non-standardised BMD)	*Z*-score	*Z*-score	*Z*-score	*Z*-score
Radius BMD	-12.9% (p=<0.01§)	-	-	-	-
Spine BMD	-	-1.75*	-1.49*	-0.87	-0.78
NOF BMD	Left: -0.3 (p=0.89) Right: -2.5% (p=0.25)	-1.70*	-1.38*	-1.81*	-1.15*
Trochanter BMD	Left: -3.5% (p=0.16) Right: -5.0% (p=0.04§)	-1.54*	-1.34*	-1.51*	-1.01*

§ denotes statistically significant result

* denotes result significantly different from reference group (patients with clinical CT examination unrelated to skeletal disease) Authors did not cite p-values

These results show that people who have fractures at a particular site also have lower BMD at that site,[6,83,84] although the findings for the lumbar spine are mixed,[6,81] possibly due to small sample sizes. Patients in these studies with one fracture sometimes had low BMD at anatomical sites other than the sites of the fracture. Of most note, men and women with spine fractures also had low BMD at the hip, but men and women with hip fractures did not have significantly lower age and gender-matched spine BMD than the reference group.[84] Results in the Ooms *et al.*[83] study are more difficult to analyse than that of Kroger *et al.*[84] because the bone density measurements were not standardised for age.

"Previous fractures" has been used as a risk factor for predicting low BMD by the use of multivariate risk factor models. Goemaere *et al.*[85] found that having a fracture after age 50 adds information to such a model (See Table 9 and also Table 28 on page 67).

Table 9 – Association between presence of wrist fractures after age 50 and BMD in women in the general population

	Site	Statistical technique	p-value
Goemaere, 1999[85] Wrist fracture after age 50	LS	Multiple stepwise regression	<0.01
	NOF		<0.01
	TF		<0.01

LS = lumbar spine, NOF = neck of femur, TF = total femur
Regression coefficients were not specified by the author

While BMD has been shown to be lower in people who have sustained a fracture, there is no one BMD cutoff that separated fracture and non-fracture cases.[86]

Conclusion

People who have already sustained a fracture are more likely to have low BMD than people who have not sustained a fracture - both in respiratory patients and patients in the general population. Low BMD at one site is also associated with low BMD at some other skeletal sites. The studies investigating associations between previous fractures and low BMD are all quite different, but the association between the two appears moderate. Therefore, utilising pre-existing fractures as a risk factor adds information to multivariate risk factor models for predicting low BMD.

2.1.7.1.4 Low levels of physical activity or periods of immobilisation

Patients who have asthma or COPD have low levels of exercise compared to normal subjects.[71] The lowest levels of daily exercise are found in the patients with the most serious respiratory disease (in this case, patients taking intermittent OCS), who also have the poorest lung function and the highest cumulative steroid dose (See Table 10). These are also known risk factors for low BMD, and will be discussed later. No studies include all three factors in a multivariate model – therefore the independent contribution of each cannot be quantified.

Table 10 – Daily exercise, lung function and cumulative steroid dose in men with COPD and normal control subjects (Iqbal, 1999[71])

	COPD Intermittent OCS	COPD ICS, no OCS	COPD No CS	Non-COPD No CS
Exercise, subjective hours walked/day	2.2±0.3‡	3.4±0.5	2.6±0.3‡	5.0±0.5
FEV^1 (% predicted)	50.6±2.8†	59.0±3.7	68.9±4.7	-
Cumulative steroid dose (μg)	4121±+617‡	430±70	-	-

‡p<0.05 vs control subjects
†p<0.05 vs COPD, no CS

While the COPD subjects as a whole had lower exercise levels than the control group, the authors did not offer any explanations for the variation in exercise levels between the three groups of patients with COPD.

In addition to low levels of exercise, people with asthma or COPD have frequent periods of immobilisation due to bed-rest during infective exacerbations of their respiratory disease. Immobilisation entails considerable loss of trabecular bone in normal subjects[87]. (~1% per week), and a sedentary lifestyle reduces skeletal loading on the bones, which may reduce bone mass over time.

Table 11 – Results from risk factor studies utilising multivariate analyses to investigate reduced physical activity as a risk factor for low BMD

Study name	Site	Variable	Analysis	Results	
Bauer, 1993[59]	Radius	Lifetime activity (intensity weighted)	% change in bone mass/unit	0.5%	
Elliot, 1993[60]	LS	Inactivity (active→ inactive)	Multiple linear regression	Men	-0.25, p<0.001
	NOF				-0.27, p<0.001
	LS			Women	-0.02, p=n.s.
	NOF				-0.14, p<0.001
Ribot, 1992[61]	LS	Immobilisation>2 months	Multiple logistic regression	n.s.	
Wong, 2000[65] ‡	LS	Exercise score (per quintile)	Regression coefficient	n.s.	
		Standing at work		0.024, p=0.061	
		Walking at work		0.021, p=0.098	
		Lifting at work		0.002, p=0.028	
Torgerson, 1995[72]	NOF	Walking (>2hr week → never)	Multiple linear regression	Rho=-0.01114,	

Epidemiological studies listed in Table 11 found associations between low levels of physical activity and low BMD in most[60,72,59] but not all[65] studies investigating physical activity and BMD by various definitions, some of which used units not readily applicable or relevant to clinical practice.[59] Only one study specifically investigated

‡ Results for Wong, 2000[65] are univariate analysis – no multivariate results were available for physical activity

activity during work time,[65] finding no association between occupational activity and low BMD.

The effect of immobilisation on BMD (using risk factor models) has been less well studied than physical activity in general. In the one study found on the topic, immobilisation for >2 months was not significantly associated with low BMD.[61] However, this patient group had few people that had been immobilised continuously for this length of time (6%), which is not unexpected for a patient group drawn from the general population.

Conclusion

Physical activity of various types appears to be associate with higher BMD, and conversely inactivity appears to be associated with low BMD. These results are consistent in men and women, and at most sites investigated, and the association appears moderate. There is insufficient data to decide what type of activity, if any, would be the best to include in a risk factor model to predict low BMD eg occupational or lifetime activity levels.

There are insufficient studies on periods of immobilisation to conclude if including immobilisation in a risk factor model for predicting low BMD would add any information not conferred by other factors.

2.1.7.1.5 Cigarette Smoking

Many patients with respiratory disease are current or former smokers.

There were no significant differences between the BMD of pre-menopausal smokers and non-smokers (0.1%, not statistically significant)

A meta-analysis of cross-sectional and cohort studies found that post-menopausal women who smoked had lower BMD than non-smokers of the same age (0.14 SD or 2%, $p<0.001$). There were no significant differences between the BMD of pre-menopausal smokers and non-smokers (0.1%, not statistically significant).[68] Results in men were not significant, but fewer studies have been undertaken and therefore there may be insufficient sample size to show an effect should it exist. The few studies that have been undertaken in men show a similar proportionate effect to that found in women. The difference between smokers and non-smokers increased linearly with age, with 2% difference between female smokers and non-smokers at menopause, which increased threefold to 6% by age 80 ($p=0.001$). Estimates were

consistent for the radius, NOF, and calcaneus. The effect of smoking on spine BMD was not investigated.

Studies that investigated associations between BMD and smoking in multivariate models are tabulated in Table 12.

Table 12 – Multivariate associations of BMD and smoking

Study name		Site		Regression coefficient	P value
Law, 1997[68] (Meta-analysis)	Never vs current smoking	(Pre-menopausal women)			
		NOF		-0.01 SD	n.s.*
		Radius			
		Calcaneus			
		(Post-menopausal women)			
		NOF		0.14 SD	<0.001
		Radius			
		Calcaneus			
Elliot, 1993[60]	Never vs ever smoking	Men	LS	-0.14	n.s.*
			NOF	-0.12	n.s.*
Nguyen, 1994[74]		Men	LS	-0.02	<0.01
			NOF	-0.02	<0.01
Elliot, 1993[60]		Women	LS	-0.118	<0.05
Nguyen, 1994[74]		Women	LS	-0.002	n.s.*
Wong, 2000[65]		LS (women & men)		0.04	0.06 (n.s.)
Torgerson, 1995[72]	Current smoker	LS		>0.01	n.s. *
Lau, 1998[88]		LS (men)		-0.024	>0.05
		LS (women)		-0.052	>0.05
Ribot, 1992[61]	Pack years	LS		>0.01	n.s.*
Wong, 2000[65]		LS		-0.02	0.22 (n.s.)
Slemenda, 1990[66]		LS		-0.00046	sig*
Stevenson, 1989[62]	Total cigarettes smoked	LS (Post-menopausal women)		-0.05	n.s.*
		(Pre-menopausal women)		-0.24	<0.025
Jones & Scott, 1999[89]	Current smoking	NOF		-0.36 SD	sig*
		LS		-0.47 SD	sig*

* authors did not specify p-value

The meta-analysis by Law *et al.*[68] concluded that smoking reduces BMD at the NOF, radius, and calcaneus in post-menopausal women, but not pre-menopausal women.[68] Since this meta-analysis was published, two large studies have showed a large effect of smoking in pre-menopausal women in Australia,[89] and Denmark,[90] with lower BMD at the NOF, LS but not at the radius. Both studies found interactions between measures of fatness (fat mass and BMI) and BMD, with lower BMD in groups with lowest BMD or fatness, consistent with earlier research.[91] Other effect modifiers include breastfeeding, sports participation,[89] and earlier menopause.[68]

Outside the meta-analysis by Law *et al.*,[68] evidence for low BMD in men is scarce, with conflicting results in the other two studies outside the meta-analysis at both the neck of femur and lumbar spine.[60,74]

Smoking is particularly important to consider in a population of people with airways disease, as the prevalence of ever smoking is high.

Conclusion

These findings show small but significant differences between the BMD of ever- and past- or never-smokers in pre-menopausal women,[89,90] (except at the spine).

If any conclusions can be drawn in men, it may be that smoking reduces BMD in older men rather than younger. Nguyen *et al.*[74] found significant associations between smoking and low BMD in their older cohort but not in the study population with a wider range of ages in Elliot *et al.*[60]

As the absolute difference between the smokers and non-smokers is small, studies with large numbers of participants, or meta-analyses required to achieve statistically significant results. However, a small effect multiplied over many smokers in both the normal population and patients with COPD or asthma means that the negative effect on BMD by cigarette consumption, is a significant public health issue.

2.1.7.1.6 Family history of osteoporosis

The genetic contribution to bone mass is high, and varies by site.[58] Therefore, investigating family history of osteoporosis as a risk factor for low BMD has face validity.

Table 13 – Association of family history of osteoporosis and BMD

Study name	Risk factor	Site	Magnitude of effect	P value	Univariate/ Multivariate
Bauer, 1993[59]			(% change in BMD)	Both <0.05 in univariate analysis	Multi-variate
	Maternal #* >50 yrs	Radius	-2.8%		
	Paternal # >50 yrs		-1.7%		
	Maternal hip # >50 yrs	Radius	-3.9%	n.s.	Univariate
	Sister hip # >50 yrs		-1.1%	n.s.	
Wong, 2000[65]	FH osteoporosis	LS	β=-0.076	0.25	Univariate
Ribot, 1992[61]	FH osteoporosis	LS	n/a	n.s.	Multi-variate
Ballard, 1998[73]	FH osteoporosis	LS & NOF	n/a	0.06	Univariate
Grainge, 1999[92]	# at any age, any female relative	LS	*T*=-1.26	n.s.	Univariate
		NOF	*T*=-2.39	0.017	
		Radius	*T*=-1.78	0.075	
	# at any age, Mother	LS	*T*=-1.56	n.s.	
		NOF	*T*=-2.89	0.004	
		Radius	*T*=-1.59	n.s.	
	# at any age, Sister	LS	*T*=-0.96	n.s.	
		NOF	*T*=-0.82	n.s.	
		Radius	*T*=-1.00	n.s.	
	# at any age, Mother or Sister	LS	*T*=-1.90	n.s.	
		NOF	*T*=-3.02	0.003	
		Radius	*T*=-1.57	n.s.	
	# at any age, other female relative	LS	*T*=+0.06	n.s.	
		NOF	*T*=-0.84	n.s.	
		Radius	*T*=-1.97	0.049	
	Low trauma fractures aged ≥50, Mother or Sister	LS	*T*=-2.15	0.032	
		NOF	*T*=-3.47	<0.001	
		Radius	*T*=-2.58	0.010	

* #= fracture
FH= family history

Of all the sites investigated, the neck of femur has the strongest association with low BMD, compared to the lumbar spine and radius, although results are mixed. The "component" of family history of osteoporosis most closely associated with low BMD are fractures sustained by the mother, either all fractures, or low trauma fractures.[59,92]

However, family history of osteoporosis is poorly associated with BMD overall. One explanation may be that "family history of osteoporosis" is a notoriously difficult risk factor to record accurately, with one research group claiming that 24% of their cohort could not remember if their mother had a fracture or not.[59] Study participants may have differences in recall as to whether or not family members had fractures or not, or may misunderstand what "osteoporosis" is (such as confusing "osteoporosis" with

"osteoarthritis"). This may result in misclassification bias, and thereby dilute the true effect of the factor towards zero so the risk factor is no longer statistically significant. An alternative explanation is that a family history of osteoporosis may not explain any extra variation in multivariate models not accounted for by other model items.

Conclusion

Of all the sites investigated, the neck of femur is most strongly associated with family history of osteoporosis or fractures (followed closely by the radius), and the best "component" to include in a risk factor model appears to be fractures sustained by the mother (all fractures, or solely low trauma fractures). There would only be benefits of including family history of osteoporosis or fractures in relatives in a risk factor model for identifying patients with low BMD if the participants' recall of their family's history of osteoporosis is reasonably accurate.

2.1.7.1.7 Calcium intake

Dietary intake of calcium is reduced in patients with respiratory disease,[64] associated with the health belief that "milk makes mucous".[93]

Table 14 – Risk factor studies investigating associations between calcium intake and bone density

	Study name	Site	Analysis method	Regression coefficient	P value
	Current calcium levels or intake				
Females	Elliot, 1993[60]	LS	Multiple linear	0.07	n.s.
		NOF	regression	0.05	n.s.
	Nguyen, 1994[74]	LS	Multiple linear	0.004	n.s.
		NOF	regression	0.01	<0.01
	Hansen, 1991[94]	LS, NOF	Univariate analysis	-	n.s.
	Stevenson, 1989[62]	Postmenopausal			
		LS	Univariate	0.07	n.s.
		NOF	correlation	0.11	n.s.
		Pre-menopausal			
		LS		0.11	n.s.
		NOF		0.13	n.s.
Females and males	Wong, 2000[65]	LS	Univariate regression coefficient	0.021	0.002
Males	Elliot, 1993[60]	LS	Multiple linear	0.07	n.s.
		NOF	regression	0.14	<0.05
	Nguyen, 1994[74]	LS	Multiple linear	0.02	<0.01
		NOF	regression	0.01	<0.01
	Total calcium intake (various sources)				
	Study name	Site	Units	%change in BMD	P value
Females	Bauer, 1993[59]	Radius		(univariate level)	
			Univariate correlation		
			Total calcium intake (current)	0.10%	n.s.
			Multivariate linear regression		(univariate level)
			Calcium from food (current)	0.70%	<0.05
			Calcium from milk (lifetime)	0.20%	<0.05

Calcium intake appears to be positively correlated with BMD. However, the effect is probably small (changing BMD by 0.1-0.7% in Bauer *et al.*[59]). Patients with asthma or COPD may require more dietary calcium than normal individuals due to inhibition of intestinal calcium absorption by glucocorticoids, which has been investigated in people taking oral corticosteroids.[95]

Conclusion

Calcium intake is associated with BMD, but the effect is small and would be detected only in large studies (such as Bauer *et al.*[59]). Of the sources of calcium, whose

relationship with BMD has been investigated, the best factor may be calcium sources from current food intake (from Bauer *et al.*[59]). No skeletal sites seem to be more strongly associated with BMD than others. Therefore, including calcium intake in a risk factor study to predict low BMD adds less information than other factors with stronger associations with low BMD.

2.1.7.2 Risk factors relevant particularly to patients with respiratory disease

These include the use of corticosteroids and poor lung function.

2.1.7.2.1 Corticosteroids

Corticosteroids are commonly used as therapy for patients with COPD and asthma, ingested either orally as tablets (prednisolone) or inhaled into the lungs using inhalers which deliver a measured dose of beclomethasone, budesonide, or fluticasone. High corticosteroid intake has been associated with low BMD. Smith *et al.*[4] summarised BMD reductions in cross-sectional and cohort studies of asthma or COPD patients taking corticosteroids in a literature review (see Table 15).

Table 15 – BMD reduction in patients with asthma and airways disease stratified for corticosteroid intake – data from Smith *et al*, 1999[4]

Corticosteroid intake	Site	% reduction compared to controls	
		Site specific	Including all sites
OCS dependent	Femur "Hip" Neck of femur Ward's triangle Trochanter Lumbar spine Forearm Total body calcium	15.5 16 22 14 8.2 – 29 15 13.6	**8-29**
ICS, some OCS	Total body calcium Lumbar spine Femur Neck of femur Trochanter Ward's triangle	8.8 6.4 - 21 8 6.6 13.2	**6-21**
ICS, no OCS	Total body calcium Lumbar spine Hip	12 0 10	**0-12**
No OCS or ICS	Total body calcium	6	**6**

"Hip" is listed where no particular anatomical segment of the femur was stated in original paper

Therefore, from the data in Table 15, there are insufficient studies to decide if BMD reduction is different between anatomical sites, although BMD reduction appears to be greatest in patients taking the highest amounts of corticosteroids, and least in patients taking the lowest amounts. Dose response and BMD or fracture risk has been studied by two separate research groups – with one investigating this dose-response effect on BMD, estimating that doubling cumulative dose of ICS decreased BMD by 0.13 - 0.18 SD at the lumbar spine and the femur in young asthmatics, concluding that the higher the amount of inhaled corticosteroids asthmatics consumed, the lower their BMD was at the lumbar spine and neck of femur.[65] Van

Staa[96] studied fracture risk (rather than BMD) and oral corticosteroid use. Relative rates of non-vertebral, hip and vertebral fractures all increased from the lowest to highest categories of daily dose of OCS, compared to age-, sex- and medical-practice matched controls, with relative risks for hip fractures 0.99, 1.77 and 2.27 for 2.5mg, 2.5-7.5mg and >7.5mg groups, and vertebral fractures having relative risks of 1.55, 2.59 and 5.18 for the same dosage groups. In addition, fracture risks declined towards baseline rapidly following cessation of OCS treatment, suggesting that increased fracture risk conferred by daily OCS use may be reversible to some extent.

Corticosteroid intake has been used as a risk factor in risk factor models for predicting low BMD (See Table 16), of which only one uses the risk factors in a multivariate analysis (Thompson *et al*[70]). More information on sampling frames of these studies are found in Table 75 in Appendix 1 on page 195.

Table 16 – Risk factor studies investigating association between corticosteroid intake and bone density

Study name	Site	Risk factor		p-value
Toogood, 1995[81]			Change in lumbar spine *Z*-score as analysed by ANCOVA	
(OCS dependent asthmatics)	LS	Daily dose ICS (mg)	↓	0.013
		Years on OCS	↓	0.032
		Cumulative dose ICS	↑	0.002
		Daily dose OCS	→	0.943 (n.s.)
Laatikainen, 1999[64]			Correlation coefficient (using BMD in g/cm^2)	
(Middle aged female Asthmatics)	LS	Duration of ICS	-0.355	p<0.001
	NOF	treatment (years)	-0.105	n.s.
	LS	ICS daily dose (mg)	-0.136	n.s.
	NOF		-0.13	n.s.
	LS	Duration of regular OCS	-0.191	p<0.05
	NOF	treatment (years)	-0.2	p<0.05
	LS	Oral corticosteroid	-0.124	n.s.
	NOF	courses (number)	+0.015	n.s.
Thompson, 1997[70]			Stepwise discriminant analysis model (using BMD in g/cm^2) which includes:	
(Post-menopausal OCS dependent Females)	NOF & LS	Years on OCS	BMI, years postmenopausal, years on OCS	p<0.01
	NOF	Years on OCS	BMI, years on OCS	p<0.01
	LS	Years on OCS	BMI	n.s.

n.s. = not statistically significant

Only two factors were studied by more than one research group – years on oral corticosteroids, (significant addition to model in all three studies), and daily dose of ICS (significant addition to model using *Z*-scores,[81] but not using BMD unstandardised for age and gender.[70]) However, the association of high cumulative dose of ICS with high bone density found by Toogood *et al.*[81] is unexpected, and the

authors suggest that the high past and current usage of oestrogen by the women in their study (41 of 43 women) might account for this finding, as oestrogen use correlated positively with higher spine *Z*-scores (p=0.049).

While observing that BMD decreased with increasing steroid intake, Smith *et al.*[4] (Table 15) also noted that subjects who had never had any ICS or OCS still had up to a 6% reduction in BMD, suggesting that corticosteroid use appears to contribute significantly to BMD reduction, but is not the only factor contributing to such an effect. Clarifying a causal link between corticosteroid intake and low BMD has been difficult due to a number of confounding variables, including the patient's underlying disease, and co-existent disease-related factors, which include differences in physical activity levels or disease severity.[97] Some of the effect of corticosteroids on fracture risk is independent of BMD,[19] probably mediated through osteocyte apoptosis,[98] thereby reducing the numbers of bone cells.

Conclusion

BMD decreases with increasing corticosteroid intake. Using measures of corticosteroid intake is useful for predicting low BMD, and the best risk factors to use in risk factor modelling appear to be daily dose of ICS, years on OCS, and duration of ICS treatment (years). Corticosteroids are not the only factor contributing to BMD reduction in respiratory patients, and confounders include the patient's underlying disease, and co-existent disease-related factors.

2.1.7.2.2 Poor lung function

Patients with respiratory disease have reduced lung function (as measured by forced expiratory volume in one second, or FEV_1), with the lowest BMD found in patients with the poorest lung function.[99,100] Worsening osteoporosis, demonstrated by thoracic wedge fractures, have been shown to further impede respiratory function in patients known to have low BMD but without respiratory disease.[101]

Packe *et al.*[99] and Praet *et al.*[100] investigated FEV_1 and BMD in respiratory patients stratified by corticosteroid usage. When FEV_1 was standardised to percent predicted, the two groups of patients were shown to be functionally equivalent for their age,[100] although the patients taking maintenance OCS had more severe disease because they required more medications to treat their respiratory symptoms.

Table 17 – FEV_1 and bone density in respiratory patients

Patient type		Maintenance OCS	ICS, intermittent OCS	No CS
Packe, 1992[99]	FEV_1 (litres)	1.86±0.53	2.62±1.14	3.34±1.00
	BMD (L1-L3 – mg/cm^3)	114.5±36.0	127.5±22.0	160.4±27.4
Praet, 1992[100]	FEV_1 (% predicted)	41±19	-	48±20
	BMD	*Z*=-1.4		*Z*=-1.0
	Number of daily medications (including CS):			
	0	0%		0%
	1 or 2	33%		84%
	>2	67%		12%

Conclusion

Low FEV_1 is associated with low BMD, and the association is moderate, although it has been investigated by few studies and is confounded by corticosteroid intake, age, and non-respiratory co-morbidities. FEV_1 is able to be easily, objectively and reliably reported in patients with respiratory disease, and despite the confounders, it may add information to a multivariate model.

2.1.7.3 Inter-dependence of risk factors

In addition to the confounders between low BMD and corticosteroids, the same phenomena observed in Guyatt's review[97] can be seen in the evidence considered earlier in this thesis. BMD decreases with advancing age (Table 3), but fracture risk increases with advancing age independent of BMD.[16,17] Advancing age also widens the BMD gap between smokers and non-smokers, and may be a marker for other factors associated with advancing age such as poor health. Patients with the poorest

lung function also have higher current dose of corticosteroids and poor general health (Table 17), which are also related to low levels of physical activity and high cumulative corticosteroid dosage (

Table 10).

2.1.8 Strength of evidence of risk factors

The strength of evidence of risk factors discussed in this review is rated as

- "Strong" (statistically significant relationship with BMD in most studies)
- "Intermediate" (Statistically significant relationship with BMD in some studies)
- "Weak" (Statistically significant relationship with BMD in few studies)

Table 18 – Strength of evidence of risk factors for low BMD

	Weak	Intermediate	Strong
Advancing age			✓
Low BMI			✓
Previous fractures		✓	
Low levels of physical activity		✓	
Cigarette smoking		✓ (Men)	✓ (Women)
Family history of osteoporosis	✓		
Low calcium intake		✓	
High corticosteroid intake			✓
Poor lung function		✓	

2.1.9 Conclusion

Risk factors for low BMD in patients with asthma or COPD include both risk factors applicable to the wider community (such as activity, corticosteroid intake, advancing age, low body weight) and also risk factors specific to respiratory disease (such as poor lung function). Both general population and disease-specific risk factors ought to be considered when designing a screening strategy to identify patients at higher risk of developing low BMD.

In people with more severe disease, the negative effect of taking corticosteroids, high alcohol and cigarette consumption may overshadow small effects of other factors eg low calcium intake on bone density.

2.2 Is early treatment for low BMD during the pre-fracture phase effective in preventing or reducing morbidity and mortality?

2.2.1 What treatments are available for preventing or reversing low BMD?

The use of numerous agents as treatments or prophylaxis for low bone density in patients with respiratory disease has been studied in three systematic reviews of trials undertaken solely in post-menopausal women,[9] and in patients taking daily oral corticosteroids.[102-104]

The studies conducted in post-menopausal women will not be discussed here, because women with secondary causes of low BMD, such as corticosteroid usage, are routinely excluded from population studies of treatments for low BMD and therefore these trials exclude the patients of greatest relevance to this thesis.

There are similar reviews of clinical trials for treatments for low BMD in patients taking daily oral corticosteroids[102,105,106] for conditions such as rheumatoid arthritis and Crohn's disease, as well as patients with respiratory disease.[105] The effect of treatments for low BMD on bone density and fractures of the hip and spine in patients taking daily oral corticosteroids is summarised in Table 19 and Table 20.

A number of studies have investigated the effect of some of these treatments on patients taking daily oral corticosteroids where none of the trial participants had respiratory disease. The results from these studies can probably be extrapolated to patients with respiratory disease. However, studies not including at least a minority of patients with respiratory disease will not be considered here in favour of studies that do. There were no studies found which investigated treatments for low BMD in patients with respiratory disease not taking daily oral corticosteroids. The pharmaceutical preparations currently available in Australia for treating low BMD are listed in Table 21.

2.2.2 Treatments investigated in groups of people taking corticosteroids

The trials discussed in this section can be found in Table 19 and Table 20 on pages 52-53.

Calcium supplementation

There have been no trials comparing calcium with placebo in corticosteroid treated patients or people with respiratory disease. Calcium supplementation decreases bone resorption, although it does not completely prevent bone loss.[107,108]

Participants who receive calcium supplements alone usually lose bone, eg Sambrook *et al.*[108] and Saag *et al.*[109] who found that patients receiving calcium plus placebo lost 1-4% of their bone density over one year at the spine and hip. Of the trials in Table 19 and Table 20 only four did not include calcium supplementation.[110-113] Therefore, it is good clinical practice to provide calcium supplementation to patients with respiratory disease, and patients receiving oral corticosteroid therapy, although it will not completely prevent bone loss, and there is no evidence that it prevents fractures.

Vitamin D supplementation

Adachi *et al*[114] investigated vitamin D supplementation, although two studies included vitamin D supplementation in addition to calcium.[115] Adachi *et al.*[114] did not demonstrate increase in BMD or reduction in fracture rates, and some subjects developed hypercalciuria. Vitamin D supplementation in addition to calcium has been suggested by some authors,[116] based on limited evidence. In summary, there is little evidence that it is beneficial to give patients vitamin D supplementation in addition to calcium.

Bisphosphonates

All bisphosphonate trials listed in Table 19 and Table 20 demonstrated increases in spine BMD, and all except oral pamidronate demonstrated reduction in spine fractures,[117] although the two bisphosphonate trials listed in Table 20 were not properly controlled trials,[112,113] and therefore their findings are less robust.[118] Of all the bisphosphonates in Table 19 and Table 20, only risedronate significantly increased hip BMD, and none demonstrated reduction in hip fractures. The most common side effects were upper GI symptoms and nausea. Etidronate can only be given cyclically as continuous usage impairs bone mineralisation.[119] There have been some safety concerns about the upper-GI side effects of bisphophonates, which is discussed further in due course. In summary, bisphosphonates (especially alendronate and risedronate) increase BMD of the spine and/or the hip, and prevent spine fractures in this patient group.

Fluoride

Fluoride (with or without phosphate or cyclical etidronate) has been studied in 5 trials in this patient group.[110,120-123] All studies showed significant increases in spine but not hip BMD, and no reductions in fractures at either the hip or spine. Side effects included GI symptoms and pain in the lower limbs.

Calcitonin

Calcitonin significantly increased spine BMD in all four trials, but not hip BMD, and did not prevent fractures of the spine or hip.[108,111,124,125] Side effects included nasal symptoms, and the nasal preparation had lower bioavailability compared to the subcutaneous route. In summary, calcitonin increased spine BMD but does not reduce fractures of the hip or spine.

Calcitriol

Calcitriol (with or without nasal calcitonin) increased spinal BMD but not hip BMD, and did not prevent fractures of the hip or spine.[108] The major side effect is hypercalcaemia, which must be monitored on calcitriol-treated patients. Therefore, calcitriol increases BMD of the spine but not hip, and does not prevent fractures at either spine or hip.

Hormonal preparations

Three different types of hormonal treatments have been studied in this population (all three in OCS-dependent respiratory patients,[126-128] see Table 20). All increased spine but not hip BMD, and none prevented fractures of hip or spine. All had small sample sizes and unusual or poor study designs. Therefore, more evidence is required before the efficacy of these treatments in this patient group is clear.

Raloxifene

The selective estrogen receptor modulator raloxifene has not been trialed in this patient group yet, but has recently shown encouraging results in postmenopausal women, increasing spine and hip BMD and reducing spine fractures.[129]

Comments on safety concerns of bisphosphonates from data collected in the general population

Bisphosphonates are associated with some reports of severe oesophagitis, as post-marketing surveillance of alendronate in the United States of America revealed cases of chemical oesophagitis in some patients.[130] However, at least 60% of the patients on whom the relevant information was available had not followed the dosing instructions correctly, and at least 14% had relative contra-indications to alendronate treatement,[130] and clinical reports of bisphosphonate-related oesophagitis appear to have declined in frequency once the importance of proper administration was explained to physicians.[131] There were no differences in the incidence of upper GI tract adverse events between the control and intervention groups in the *large* trials of

bisphosphonates in post-menopausal women.[132-137] Results from endoscopy trials that evaluated gastro-oesophageal lesions before, after and during alendronate and risedronate treatment showed that none detected any increase in incidence of oesophageal lesions.[131] Information about gastric side-effects of bisphosphonates has been conficting,[131] with the one double-blind placebo controlled endoscopy study of alendronate, risedronate and placebo over 28 days showing similar potential for gastro-duodenal irritation at the dosage levels approved for Paget's disese.[138] However, two 2-week non-placebo controlled endoscopy studies showed that risedronate is associated with significantly lower incidence of gastric ulcers and lower gastric endoscopy scores than alendronate, showing better condition of the oesophagus.[139,140] However, asymptomatic endoscopic lesions, like mild upper GI symptoms, are relatively common and generally fail to predict ulcer-related events.[141] [142] Upper GI tract adverse events reported during therapy may reflect a high background incidence of upper gastro-intestinal tract complaints, and an increased sensitivity to detection rather than a causal relationship to therapy,[143] and rechallenge studies have shown that most patients who previously reported intolerance to open-label bisphosphonates were subsequently able to continue treatment, and the tolerability profile was similar to placebo.[143,144] Therefore, bisphophonates are well-tolerated overall, but both doctors and their patients need to remain vigilant to make sure patients are taking their bisphosphonates.

Conclusion

All treatments listed in Table 19 significantly increased spinal BMD, although only three (intermittent cyclical etidronate, alendronate, and risedronate) demonstrated a statistically significant decrease in fracture rates at the spine. Most drug trials other than studies trialing bisphosphonates had small number of participants, thereby reducing the likelihood that the trial would demonstrate reduction BMD increases or reduction in fracture rates at non-spine anatomical sites. Risedronate is the only treatment in Table 19 to increase BMD of the hip, although this did not translate to a decrease in hip fractures. The bisphosphonates are well-tolerated, but have been associated with some upper GI side effects. Therefore, of the treatments reviewed in Table 19 and Table 20, the bisphosphonates appear to have the greatest effect in preventing bone loss and reducing fractures. However, alendronate has been associated with erosive contact oesophagitis, and therefore caution should be exercised in prescribing alendronate to patients with existing GI symptoms or people prescribed medication for GI symptoms, or with more severe underlying disease or

several co-morbidities other than their respiratory illness. These severe side effects of alendronate (gastritis and oesophagitis) are rare in post-menopausal women in the large randomised trials eg Liberman *et al.*[145] but more troublesome in patients seen in regular clinical practice,[146] possibly due to differences between ordinary patients and patients selected for clinical trials,[147] such as number and severity of co-morbidities, or the patients' commitment to the study. Of all the bisphosphonates, risedronate has both good results in increasing BMD of the hip and spine, and the best safety and tolerability profile.

Table 19 – Summary of treatments for low BMD in patients taking daily oral corticosteroids*

		Vitamin D	Bisphosphonates				Fluoride			Calcitonin	Calcitriol
		Vitamin D	Oral pamidronate (APD)	Intermittent cyclical etidronate	Alendronate	Risedronate	Fluoride	Fluoride + etidronate	Mono-flouro-phosphate	Nasal calcitonin + calcitriol	Calcitriol
Study name		Adachi, 1996[114]	Reid & Heap 1988[118], Reid & King, 1988[117]	Roux, 1998[148] Adachi, 1997[149] Skingle, 1997[150]	Saag, 1998a[109] Saag 1998b[151]	Cohen, 1999[115] Wallach, 2000[152]	Greenwald, 1992[110]; Lems, 1997a[120]	Lems, 1997b[121]	Rizzoli, 1995[122]	Sambrook, 1993[108]	Sambrook, 1993[108]
N of patients		61	40	296	477	737	54	47	48	63	63
N of studies		1	1	3	1	2	2	1	1	1	1
Studies demonstrating increased BMD	Hip	-	-	-	-	2	-	-	-	-	-
	Spine	-	1	3	1	2	2	1	1	1	1
Studies demonstrating decreased fractures	Hip	-	-	-	-	-	-	-	-	-	-
	Spine	-	-	2	1	1	-	-	-	-	-
Side effects		Hyper-calciuria	Mild nausea	upper GI symptoms	upper GI symptoms	upper GI symptoms	GI symptom, "lower extremity pain syndrome"			GI & nasal symptoms	GI symptoms, hypercalc-aemia
Costs (p.a)		n/a	n/a	$281.50	$ 747.00	$ 691.44	n/a	n/a	n/a	n/a	$ 227.21
Comments		Not true random-isation		Skingle, 1997[150] - patients withdrawn if OCS dose dropped below 5 mg/day		2 centres of same trial	Greenwald, 1992[110] not randomised				

* All studies included some number of respiratory patients, n/a = not available in Australia

Table 20 – Summary of treatments for low BMD in respiratory patients taking daily oral corticosteroids*

		Bisphosphonates		Fluoride	Calcitonin		Hormonal preparations		
		IV pamidronate	EHDP (non-cyclical etidronate)	Monoflouro-phosphate	Sub-cutaneous	Nasal	Medroxy-progesterone acetate	Estrogen/ Progesterone	Testosterone (Sustenon)
Study name		Gallacher, 1992[113]†	Worth, 1994[112]	Guaydier-Souqieres, 1996[123]	Luengo, 1990[124]	Bohning, 1990[111] Luengo, 1994[125]	Grecu, 1990[126]	Reid, 1996[127]	Lukert, 1992[128]
Number of patients		17	33	28	62	80	23	15	16
Number of studies		1	1	1	1	2	1	1	1
Studies demonstrating increased BMD	Hip	-	-	-	-	-	-	-	-
	Spine	1	1	1	1	2	1	1	1
Studies demonstrating decreased fractures	Hip	-	-	-	-	-	-	-	-
	Spine	1	1		-	-	-	-	-
Side effects		Pyrexia	Nausea	GI symptoms, pain in lower limbs	facial flushing, nausea, vomiting	rhinorrhea, nausea, facial redness, pruritus	-	-	Increase in physical strength & libido
Costs		n/a	N/a	n/a	n/a	n/a	$194.04	$87-194	$65.72
Comments		Uncontrolled trial	Not randomised	Randomised crossover study		lack of bioavailability	Not blinded	retrospective cohort study	

† compared to baseline

* All studies included some number of respiratory patients

Even groups known to be at high-risk of developing low BMD (such as people taking oral corticosteroids regularly, or people with asthma or airways disease) have difficulty accessing treatments for low BMD. Of the treatments currently available in Australia (See Table 21), all treatments except for testosterone and calcium require a prior fracture (defined as loss of vertebral height of >20% on X-ray) before the patient can obtain the authority script required to buy the medications at PBS prices. If no fracture is demonstrated on X-rays (as yet), and the patient wants to take the medication, they must pay $227-747 per annum to obtain the treatments. This is out of the financial reach of a large section of the community who would benefit from treatments as they have a very high probability of sustaining a fracture. Published cost-effectiveness analyses show that treating women over 65 years of age with low BMD and at least one vertebral fracture for 10 years is cost-effective,[153] and reduced the proportion of patients utilising health care resources.[154] In corticosteroid-treated women with rheumatoid arthritis, treating women with *T*-scores <-1 was found to be cost-effective compared to "watchful waiting",[155] as were treating various other groups of corticosteroid-treated people with low BMD but no fractures.[156] Therefore, these analyses show that alendronate treatment is most cost-effective in groups at high risk of developing fractures, not necessarily just people with existing fractures. Therefore, broadening the range of patients who can access bisphosphonates such as alendronate through the PBS may also be cost-effective.

Table 21 - Drugs available in Australia under the Pharmaceutical Benefits Scheme for treating low BMD (July 2002)[157]

Drug	Amount in pack	Cost per pack	Yearly cost (A$)	PBS Authority Indications	Available to which gender	Medium of delivery
Calcium						
Calcium 600 mg (Castrate)	120	$12.33	$36.99	"Osteoporosis"	Both	Oral
Calcium 500 mg (Calsup)	120	$12.51	$37.53	"Osteoporosis"	Both	Oral
Calcitriol (Rocaltrol)	100	$62.25	$227.21	20% loss of vertebral height	Both	Oral
Bisphosphonates						
Didrocal (etidronate 200mg + calcium 500mg)	28 etidronate, 76 calcium	$80.43	$281.51	20% loss of vertebral height	Both	Oral
Alendronate 10 mg (Fosamax)	30	$62.25	$747.00	20% loss of vertebral height	Both	Oral
Risedronate 5mg (Actonel)	28	$57.62	$691.44	20% loss of vertebral height	Both	Oral
Hormonal preparations						
Testosterone						
Sustanon 100 mg	3	$16.43	$65.72	"Androgen	Men	Injection
Sustanon 250 mg	3	$31.27	$125.08	deficiency"		Oral
Progestogen	1	$16.17	$194.04	"Off label"*	Women	Injection
Medroxyprogesterone	5mg (56)	$13.49	$87.98	prescribing		Oral
acetate (Ralovera)	10mg(30)	$14.12	$171.91			Oral
Selective estrogen receptor modifiers						
Raloxifene 60 mg (Evista)	28	$60.47	$725.64	20% loss of vertebral height	Women	Oral

*= Authority not required for prescription

Conclusion

There are a number of treatments available for preventing osteoporotic fractures that have been trialed in patients with respiratory disease, and people requiring daily oral corticosteroids. The most effective treatments are bisphosphonates (especially risedronate and alendronate). Most of the treatments studied in people taking daily oral corticosteroids (including people with respiratory disease) are available in Australia, but most treatments available are very expensive for the majority of patients who are not able to meet the PBS authority indications to receive the treatment at a subsidised price.

2.2.3 Utilisation of available treatments for low BMD in people with respiratory disease

Rates of prophylaxis for low BMD and bone density testing have been investigated in patients taking maintenance doses of oral corticosteroids. Patients identified through tertiary hospitals in the United States of America, the United Kingdom, and Australia had prophylaxis rates of 6-58%,[158-162] while patients surveyed through general practice in the United States of America, and the United Kingdom had prophylaxis rates of 14-55%.[163-165]

An estimated 27-31% of patients identified through hospital outpatient clinics[159 165 166] and 16% of patients identified through general practice had undergone bone density testing.[164] In another study, 23% of respiratory patients taking continuous oral corticosteroids received any drug therapy for low BMD, 35% had bone density testing and 55% had "any intervention" (this was a group which pooled interventions, including drug therapy, and recommendations for weight-bearing exercise);[165] other estimates show that low BMD was considered in 48% of respiratory patients taking continuous oral corticosteroids.[166] No estimates are available for patients with respiratory disease not taking continuous oral corticosteroids.

A cross-sectional study of patients presenting to orthopaedic clinics for low trauma wrist fracture estimated that 29% of patients received "any osteoporosis management" prior to the fracture. This included physician discussion regarding low bone density, or referral for BMD testing. Post fracture, 38% were taking hormone replacement therapy (HRT) or bisphosphonates, and 62% were taking calcium or vitamin D. These rates of prophylaxis were similar to that prior to fracture, indicating that the presence of a fracture does not influence the prescribing of interventions for preventing or treating low BMD. Half the patients (50%) received osteoporosis follow-up, which included discussion with a physician regarding low bone density.[167]

2.2.4 Utilisation of screening technology for identifying low BMD in people with respiratory disease

Offering bone density screening by DXA has been investigated in one RCT only. Torgerson *et al.*[168] randomised 1,600 peri-menopausal women to either screening or no screening, and subsequently recommended that women with bone density in the lowest quartile of the screened group commence taking HRT. Screening increased HRT use by around 7% (p=0.02), but no reduction in fracture rates was seen, although this would have been unlikely to be achieved, given the low fracture rate

(participants aged 45-54), small sample size (799 women randomised to screening) and short period of follow up (2 years).

Jones *et al.*[89] also screened pre-menopausal women for low BMD, although as part of a cohort study, and without a placebo group for comparison. They provided feedback on BMD results, notifying women with *T*<-1.0 that they had low BMD. Compared to women with "normal" BMD (*T*>-1.0), those with "Low" BMD (*T*<-1.0) were more likely to increase calcium intake, usage of calcium supplements, and physical activity, and there was no impact on smoking cessation.

Despite forecasts of large lifetime fracture risk and sizeable fracture burden in people with respiratory disease, rates of treatment for low bone density in airways disease are minimal, whether that treatment is taken as prevention, or if low bone density has already been identified. Most patients (40-94%)[158-162]) were not offered prophylactic treatment, and in half the patients (52%) a diagnosis of low BMD was not even considered.[166] However, evidence from the screening trial of Torgerson *et al.*[168] and bone density feedback study[89] are encouraging, suggesting that if patients receive bone densitometry and are found to have low BMD, they are more likely to make lifestyle changes to reduce some risk factors, or to take treatment for low BMD. If this were applied to other patient groups such as patients with respiratory disease, the increase in participation in bone densitometry and subsequent reduction in risk factors and increase in treatment for low BMD may result in a reduction in the rate of clinically important fractures in patients with respiratory disease.

2.2.5 Conclusion

- There are numerous anti-osteoporotic treatments available in Australia for increasing BMD and preventing fractures. Of those investigated in people taking oral corticosteroids (especially with respiratory disease), the bisphosphonates appear most effective
- Effective pharmacological treatments available today in Australia are expensive for all except the patients at extremely high risk of future fractures
- Rates of prophylaxis for low BMD are currently low. However, screening has been shown to change health related behaviours, and increase the uptake of treatments for low BMD
- Therefore, treatment to increase BMD before fractures occur is likely to prevent morbidity and possible mortality from low BMD in people with respiratory disease

2.3. Is a screening test available that is reasonably inexpensive, safe and acceptable to patients?

Many tests are available for determining BMD, such as single photon absorptiometry (SPA), single X-ray absorptiometry (SXA) dual X-ray absorptiometry (DXA), dual-photon absorptiometry (DPA), quantitative computed tomography (QCT), and radiographic absorptiometry (RA) (See Table 22). DXA has the advantage of being able to measure BMD at the hip and spine as well as peripheral sites (such as the radius). This is advantageous because BMD measurements at a given site (such as the hip), are the best predictor of fracture risk at that site, although the BMD at one site are highly correlated with BMD at other sites – for example, the correlation between the spine and neck of femur is r=0.76.[169] DXA is now the most widely used technique for measuring bone density in clinical trials and epidemiological studies due to low radiation dose per test, wide availability, and ease of use,[170] and good precision and accuracy, increasing the likelihood that changes detected in BMD over time are meaningful. DXA is currently the "gold standard" technique in use in Australia for measuring BMD.[171]

Table 22 – Comparison of bone density measurement techniques (Adapted from Eddy, 1998[9].)

	Scan charges (US$)[§]	Site/scan time (mins)	Precision error (%)	Accuracy error (%)	Radiation exposure (mrem)
SPA/SXA	50-150	Radius, calcaneus 5-15	1-3	3-8	~1
DPA	150-300	Spine, hip 20-40	2-5	3-10	~1-5
DXA	100-200	Spine, hip, radius 5-10	1-2	3-9	~1-5
QCT	150-300	Spine, hip, radius 10-30	2-4	5-15	~50
RA	75-150	Hands 5-10	1-2	5-10	~5
Annual background radiation[172]	-	-	-	-	2000

§A$1≅ US$0.5

The measurement of bone density using DXA is precise, but extremely high precision is required if DXA is to identify very small changes in bone density, which would occur if sequential scans take place over a short period of time (such as 6 months), or if the rate of change of bone density is low. In sequential monitoring, the largest component of variation is unalterable instrument-related factors(such as analysis

software),[173] although interaction between subjects and operators (such as positioning errors) also contributed significantly to variation in bone density.

Table 23 – Costs of selected radiological tests[13]

Test name	Cost †	Medicare Rebate	Final cost to consumer
Abdominal CT (including contrast)	$480	$429	$51
Mammogram (2 breasts)	$82	$69	$13
DXA	$81	$68.85	$12.15

† All costs are in Australian dollars

DXA tests are inexpensive, however, the costs of the individual tests must not be viewed in isolation as they are more important when considered as component costs of a screening program, for which estimates such as life years gained (LYG) and quality adjusted life years gained (QALY's) are obtained.

2.3.1 Body weight and size and DXA methodology

There has been increasing interest in recent years in the link between BMD measurement by DXA (the current "gold standard" technique for measuring bone density[171]) correlations between body mass parameters, such as body mass index.

Weight and BMI are certainly positively correlated with BMD,[71,65,64] and low BMI has been associated with increased risk of fractures of the hip,[77,79] wrist and ankle,[174] with every increase of 10kg/m^2 conferring a decrease in hip fracture risk of 40% (RR=0.58 (CI 0.36-0.92).[79]

However, the biological plausibility of the association has been questioned because no mechanism sufficient to explain the association has been proposed. Associations between low BMI, low bone mass, and an increased rate of bone loss were independent of age or years since menopause.

It has been postulated that there are inaccuracies inherent to *in vivo* BMD, and that the source of these inaccuracies is derived from the "two-component DXA limitation", in which DXA is unable to distinguish more than two absorptiometrically dissimilar mediums in the region of interest.[175-177] All bone sites are comprised of more than two different types of tissue eg bone mineral, lean muscle tissue, fat mass, as well as red and yellow bone marrow. Therefore, *in vivo*, DXA cannot completely satisfy the "two component" methodological limitation, and therefore must be inaccurate in measuring "true" bone density to a greater or lesser degree, and the key to DXA inaccuracies seems to be in the bone marrow and the extra-osseous fat-to-lean soft

tissue areal density ratio.[178] Simulation studies undertaken *in vivo* at the lumbar spine and femur showed that patient-specific in vivo inaccuracies exceed ±20%, and that these inaccuracies are likely to be largest in postmenopausal, osteopenic, osteoporotic and elderly individuals[179-181] - exactly the groups in which accurate estimates of BMD are the most important. These claims may seem simply incredible, as they are at odds with the general understanding of the extent of inaccuracies in DXA measurement of BMD (See Table 22). However, the body of research into inaccuracies inherent in the measurement of BMD is sound and careful research that is not easily dismissed.

The implications for a screening study are:

1. whether or not the measurement of BMD by DXA is undermined and if so, is it important
2. what potential alterations should be made as to what risk factors are included in screening models.

Therefore, there appear to be systematic errors in the measurement of bone density using DXA. However, the accuracy of bone density measurements are difficult to achieve as the experimental design does not lend itself to continuous evaluation of results available in standard laboratory practices for measuring chemicals, and no universal calibration standards are currently available. DXA is still the most dependable current technique for measuring bone density, and is still a useful surrogate marker for fracture risk, because it is a stronger long-term predictor of fractures per standard deviation change (relative risk 1.5-2.0) than markers used for other common diseases, such as cholesterol measurements for cardiovascular events (relative risk 1.3).[182]

Given the findings listed above, weight and BMI may be more accurately described as confounders rather than risk factors for low BMD. Therefore, in a screening study, weight or BMI should be measured - either as a risk factors or potential confounders, until such time as a better measure of true BMD other than DXA is found.

Conclusion

DXA tests are cheap, safe, widely available, and the most dependable technique currently available.

2.4 Does the screening test have adequate predictive value?

2.4.1 How do we decide which patients are at the highest risk, and what is the best way to identify them?

Treating a patient with low BMD to prevent a fracture is clearly the last stage in a series of steps or decision pathways, which begin with the decision by the clinician to refer the patient for bone densitometry (See Figure 1).

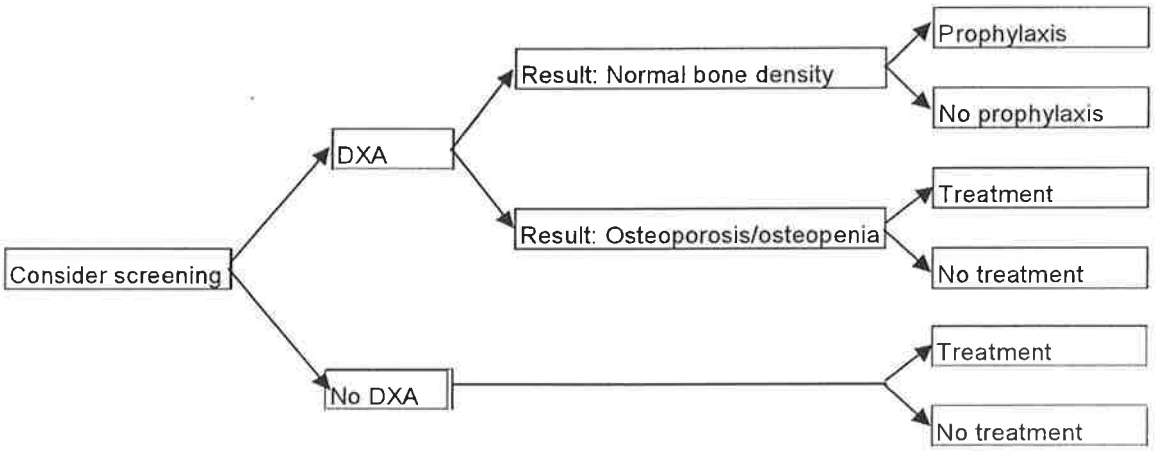


Figure 1 – Nomogram for flow of steps in diagnosing and treating low bone density

Some guidelines would not recommend densitometry unless the results could influence a treatment decision,[9,183] on the premise that the inconvenience, risks and costs of testing would outweigh the benefit of improved health outcomes[9]. In these cases, the decision to treat would be based on non-BMD risk factors, and on the benefits, risks and costs of the treatment. However, assuming that the patient would benefit from treatment, asking the patient to attend densitometry would enable monitoring of the effects of any treatment, or assess the rate of decline in BMD in these patients, even if the densitometry result would not have altered the treatment the patient received.

Examples of recommendations for which patients in the general population,[184-186] and patients with medical conditions requiring regular corticosteroids[187-189] should be sent for screening DXA are tabulated in Table 24.

2.4.2 Current recommendations for identifying patients to refer for bone densitometry

Table 24 – Summary of guidelines for identifying patients to refer for bone densitometry

Guideline	Population	Recommendation
US National Osteoporosis Foundation[184]	General population	Women over 65; minimal trauma fracture >40 years; family history of fracture; current cigarette smoking; weight <57.6 kg; used HRT for prolonged periods Bone densitometry only recommended for women who would consider therapy if appropriate
Australian Fracture Prevention Summit[183]	General population	Population screening is inappropriate. Bone densitometry only recommended for people who would consider therapy if appropriate. Recommend DXA as part of patient care rather than screening. Recommend DXA for high risk groups who can obtain Medicare rebate[13], or low body weight, low calcium intake, minimal physical activity, family history of osteoporosis, falls
NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy[186]	General population	Recommend individualised approach with current evidence. Consider DXA in patients: taking corticosteroids for >2 months, or who have other conditions "high risk" for osteoporosis (authors did not specify)
American College of Rheumatology Task Force on Osteoporosis Guidelines[187]	Patients taking corticosteroids	Patients with non-traumatic fractures, or commencing long term corticosteroid therapy
UK Consensus Group on management of glucocorticoid-induced osteoporosis: an update[188]	Patients taking corticosteroids	taking ≥7.5mg/day OCS for ≥ 6 months
Panel of allergists/immunologists (literature review)[189]	Asthmatics taking cortico-steroids	Consider DXA - asthmatics taking ≥800 mg/day beclomethasone dipropionate (or equivalent) Recommend DXA – daily OCS for 4 weeks or more OR 4 week-long courses of OCS in 1 year

The recommendations of the evidence-based guidelines listed above can be summarised as recommending that patients should undergo screening DXA if they have "risk factors" for low bone density, or receive daily oral corticosteroids. However, there is no consensus as to what constitutes a "risk factor" for low bone density, and the NIH guidelines[186] are very vague about their recommendations about what constitutes a "high risk" condition for low BMD. Also, the evidence basis of many of the guidelines is informal, with some not using in-text citations to reference articles, instead listing references at the end in a bibliography,[186,184] leaving the reader unsure of the origin of the supporting evidence for their recommendations. The action(s) recommended by the guidelines in Table 24 (that people at increased risk of having low BMD should have their low BMD confirmed (by DXA), and then

should receive treatment to increase their BMD) are in sharp contrast to what is occurring in clinical practice. BMD tests had taken place in an estimated 16-31% of patients receiving daily oral corticosteroids,[166,159,164,165] and up to 27% in patients with minimal trauma wrist fractures[167] whereas the guidelines would have recommended that all patients taking OCS for 1-6 months should have a DXA.[186,188,189] A time lag between the publication of research findings and the implementation of the research into clinical practice is unlikely to account for the discrepancy, given the recent nature of these studies.[158-167]

Conclusion

The guidelines listed in Table 24 correctly identify patients at high risk of osteoporotic fractures and low BMD. However, the actions they recommend are inconsistent. In addition, the approach of "case finding" by individual physicians implicit in these guidelines is not succeeding because the recommendations are not being carried out in clinical practice.

2.4.3 Systematic approaches to identifying patients at high risk of low BMD

A more systematic approach using pre-screening techniques to separate those at high and low risk of having low BMD has been suggested. This would complement existing "case-finding" strategies by physicians by identifying higher-risk populations to whom screening could be targeted.

Pre-screening questionnaires such as the Simple Calculated Osteoporosis Risk Estimation (SCORE)[190] in Table 25 combine a short-list of known risk factors for low bone density into a questionnaire that can be easily and quickly completed by either patient or clinician from readily available information. If the patient has a score above a pre-determined threshold (the authors recommend ≥6), then the patient is recommended to have bone densitometry. The SCORE questionnaire has been well validated with sensitivity of 88-99% and specificity of 12-51%[190-195] (See Table 27).

Table 25 – Scoring system for SCORE†

Variable	Score	If woman:
Race	5	Is NOT black
Rheumatoid arthritis	4	HAS rheumatoid arthritis
History of fractures	4	For EACH type of fracture (wrist, rib, hip) of non-traumatic fracture after age 45 (Maximum score=12)
Age	3	Times first digit of age in years
Estrogen	1	If NEVER received estrogen therapy
Weight (in pounds)	-1	Times weight divided by 10 and truncated to integer

† Women with SCORE>6 would be selected for densitometry
See example[§]

The Osteoporosis Risk Assessment Instrument (ORAI)[196] is a similar type of pre-screening questionnaire to SCORE, but without the risk factors race, rheumatoid arthritis, or fracture history (See Table 26).

Table 26 – Scoring system for the ORAI

Variable		Score‡
Age, year	≥ 75	15
	65-74	9
	55-64	5
	45-54	0
Weight, kg	<60	9
	60-69	3
	≥70	0
Current estrogen use	NO	2
	YES	0

‡ Women with a ORAI> 9 would be selected for bone densitometry
See example[§]

[§] For example, a 70kg (=154 lb), 70 year old white woman without rheumatoid arthritis, who had not had a fracture after age 45, and was taking oestrogen, would be recommended for densitometry as she has a SCORE of 11, which is greater than the cutoff of 6. [(5+0+0+(3x7)+0–15)=11]

ORAI has not been as well validated as SCORE, and has lower reported levels of sensitivity (80-89%) but similar ranges of specificity (32-48%)[196,195] (See Table 27).

Cadarette *et al.*[195] assessed the diagnostic properties of 4 decision rules – SCORE[190], ORAI[196], ABONE[197], and body weight ≤70kg,[198] plus the WHO definitions of osteoporosis and osteopenia.[12] They found that the area under the receiver operating characteristic (ROC) curve was greatest using SCORE and ORAI, and at 90% sensitivity, SCORE had slightly better specificity than ORAI for this population (SCORE specificity ~50%; ORAI specificity ~35%), and therefore of the tests developed so far, SCORE is the best at discriminating patients with and without low BMD.

Sensitivity and specificity of the published studies that have used SCORE are tabulated in Table 27.

[§] The woman described on the previous page who would be selected for densitometry using SCORE would also be selected for densitometry using ORAI (70 years of age, currently using oestrogen, weight 70kg), has an ORAI of 9, which is equal to the cutoff for DXA which is 9 [9+0+0=9]

Table 27 - Models for predicting low bone density; SCORE and SCORE validations[Ω].

Study	Participants	Criteria, SCORE threshold	Site	Sensitivity (%)	Specificity (%)	% saving by using model	Area under curve (AUC)
Lydick, 1998[190]	Community dwelling peri-and post-menopausal women 50% from tertiary referral centre	*T*<-2.5, threshold of 7 (N=1102)	NOF	94	43		0.77
		T<-2, threshold of 6 (N=185)	NOF	89	50	30%	-
		Linear Model (N=816)	NOF	90	47		0.81
Cadarette, 1999[191]	Community dwelling post-menopausal women. Subset of Cadarette, 2000[196] population	*T*<-2; SCORE=6 (N=398)	LS/NOF	90	32	32%	0.71
		T<-2; SCORE=6 (N=397)	NOF	90	29	-	-
		T<-2; SCORE=6 (N=396)	LS	93	26	-	-
Von Muhlen, 1999[192]	Community dwelling older Caucasian women (N=1013)	*T*<-2; SCORE=6	NOF	98	13	55%	0.70
		T<-2; SCORE=11	NOF	80	45	28%	-
Ungar, 2000[193]	Women from tertiary referral centres	*T*<-2; SCORE=6, 50-59 yrs	LS/NOF	96	51	-	-
		T<-2; SCORE=8, 60-70yrs	LS/NOF	90	20	-	-
Russell, 2001[194]	Sample of women presenting for bone density test	*T*<-2.5; SCORE=6	NOF	99	27	22%	-
		T<-2.5; SCORE=6	LS	96	28	20%	-
		T<-2.5; SCORE=10, age ≥65 (N=54)	NOF	88	35	27%	-
Cadarette, 2001[195]	Includes population of Cadarette, 2000[196] (N=2365)	*T*<-2.0; SCORE=6	NOF	98	21		0.77
		T<-2.5; SCORE=6	NOF	99.6	18		0.80

[Ω]Model includes race, rheumatoid arthritis, fracture history, age, estrogen, weight

Table 28 - Models for predicting low bone density (non-SCORE)

Study	Participants	Criteria	Site	Sensitivity (%)	Specificity (%)	% saving by using model	Area under curve (AUC)	Model includes
Elliott, 1993[60]	Female							age, weight, ever smoked, age at menarche
	Volunteers (N=320)		LS	92	31		-	
	Electoral Roll (N=107)		LS	86	32			
	Female							age, weight, family history, inactivity, ever smoked
	Volunteers (N=320)		NOF	91	29		-	
	Electoral Roll (N=107)	Top 2/3 compared to bottom 1/3	NOF	89	25	10-23%		
	Males							weight, inactivity
	Volunteers (N=131)		LS	91	30		-	
	Electoral Roll (N=126)		LS	83	46			
	Males							age, weight, family history, inactivity, weekly calcium intake
	Volunteers (N=131)		NOF	88	42		-	
	Electoral Roll (N=126)		NOF	87	45			
Ballard, 1998[73]	Elderly women N=823	*T*<-2.5		92	32		0.73	
		# suspected from x-rays (40% of sample)		70	51		-	
		Forearm # from simple fall (43% of sample)	LS or NOF	66	54		-	Weight, age at menopause, current HRT use
		All # from simple fall (47% of sample)		60	58		-	
Goemaere, 1999[85]	Postmenopausal women from general practices N=300	*T*<-2.5, score=8.6	LS	62	62		0.66	Race; height; age; weight; intake of: cigarettes, caffeine, alcohol, dairy, sun, exercise; medication use; previous #; FH of osteoporosis; age at menopause
		T<-2.5, score=8.6	NOF	62	65		0.69	
		T<-2.5, score=9.3	TF	63	75		0.76	
"Body weight criterion", Michaëlsson, 1996[198]								
Michaëlsson, 1996[198]	Women from electoral roll (N=175)	*T*<-2.5	LS	89	38			Weight ≤70kg
		T<-2.5	NOF	94	36	33%		
Cadarette, 2001[195]	Includes population of Cadarette, 2000[196] (N=2365)	*T*<-2.0	NOF	80	52		0.74	
		T<-2.5	NOF	87	48		0.79	
Osteoporosis Risk Assessment Instrument (ORAI) – Cadarette, 2000[196]								
Cadarette, 2000[196]	Community dwelling peri-and post-menopausal women (sex-, region-stratified random population sample) (N=924)	*T*<-1; ORAI=3	LS	81	46			Weight, age, current estrogen use
		T<-1; ORAI=3	NOF	80	43			
		T<-2; ORAI= 9 (N=924)	LS or NOF	90	45	32%	0.789	
Cadarette, 2001[195]	Includes population of Cadarette, 2000[196] (N=2365)	ORAI						
		T<-1; ORAI= 9	NOF	94	32		0.76	
		T<-1; ORAI= 9	NOF	98	48		0.79	
Age, Bulk, and One or Never Estrogens (ABONE) –Weinstein, 2000[197] §								
Cadarette, 2001[195]	Includes population of Cadarette, 2000[196] (N=2365)	*T*<-2.0; ABONE≥2	NOF	79	53		0.71	Weight, age, estrogen use
		T<-2.5; ABONE≥2	NOF	83	48		0.72	
National Osteoporosis Foundation criteria[184]								
Cadarette, 2001[195]	Includes population of Cadarette, 2000[196] (N=2365)	*T*<-2.0; NOF≥1	NOF	94	21	0.67		Age, weight, minimal trauma fracture, family history of fractures, cigarette smoking
		T<-2.5; NOF≥1	NOF	96	18	0.70		

§ Original paper describing ABONE by Weinstein, 2000[197] did not report the sensitivity and specificity of the screening tool
#= fracture

If studies with sensitivity ≥90% are considered, the corresponding specificity of SCORE is 13-51%, with 20-55% of patients able to be excluded from densitometry.

Many non-SCORE questionnaires did not reach the target 90% sensitivity usually aimed for in screening tools[190] which minimises the number of people whose low BMD was not identified by the test. The non-SCORE questionnaires that did have sensitivity over 90% had corresponding specificity of 30-45%, with 10-33% of patients being able to be excluded from densitometry (Table 24). Therefore, at high sensitivity, specificity of these pre-screening questionnaires is poor, with many participants with normal BMD recommended for screening DXA. Receiving a recommendation for densitometry may result in significant societal burden. This includes increased anxiety in women recommended for DXA, as they consider the possibility of an abnormal result; and also for the funding body who finances the DXA's, as many tests will be performed on women who do not benefit from the intervention.

However, even though these screening tools only reduce the number of women referred for densitometry by 10-33%, these screening tools may prove to be a cost-effective addition to bone densitometry. Using SCORE as a pre-screening tool prior to DXA in one study reduced the number of patients who required densitometry by 21%. They did this by eliminating those with SCORE<6 and giving densitometry only to those with SCORE>6. This reduced the cost per patient by US$38 (or 19%), while trading off only 2% in sensitivity (84% sensitivity) to give DXA (of the radius as well as hip and spine) to all patients, and 82% sensitivity to give hip and spine DXA to those with SCORE>6).

Few risk factors relevant to COPD-specific factors were explored in the studies summarised in Table 27 and Table 28. One explanation may be that many of the screening tools used *T*-scores (standardised to the young adult mean), making the inclusion of age-related risk factors over disease-specific factors more likely. Also, the populations in which the tools were developed were otherwise healthy postmenopausal women, with very low or zero prevalence of asthma or COPD. However, prevalence of rheumatoid arthritis was high (5-24%) in the cohorts of the initial SCORE study,[190] as one of the source groups of the study was rheumatology outpatients, and this may have contributed to the presence of rheumatoid arthritis being selected as one of the components of SCORE. Presence of "rheumatoid

arthritis" is confounded by many variables, such as corticosteroid intake, or reduced mobility levels. The inclusion of this factor is relevant for future risk factor studies in respiratory patients because of many similarities in these confounders between respiratory and rheumatology patients.

Conclusion

Evidence-based systemic approaches to identifying high-risk subgroups for low BMD prior to densitometry have been investigated. Most non-SCORE questionnaires did not reach the target of 90% sensitivity, but SCORE validations did in most populations studied. These screening tools may prove to be a cost-effective addition to densitometry by reducing the number of patients requiring densitometry by 10-33%.

2.5 General conclusion

- Low bone density causes sufficient mortality and morbidity because of its' association with fractures to warrant routine screening since the magnitude of the problem is large, both in the general population and also in people with asthma and airways disease.
- Early treatment for low bone density during the pre-fracture phase of the condition is effective in preventing or reducing morbidity and mortality, which have been studied in and are available to patients with asthma or airways disease.
- Screening DXA's are widely available, reasonably inexpensive, safe and acceptable to patients for diagnosing low bone density
- Evidence based, systemic approaches to identifying high-risk subgroups for low bone density prior to densitometry have been investigated, and these screening tools may prove to be cost-effective additions to densitometry.

Chapter 3 – Methodology of the development of a risk factor analysis to develop a screening tool to identify patients with respiratory disease who are at increased risk of low bone density

3.1 Recruiting

We collected data from patients according to the flow chart in Figure 2. Patients were recruited from metropolitan hospitals (outpatients and inpatients), and from general practices and the community in general. People who met the criteria of the pre-screening questionnaire (see also Table 32 and Appendix 2) were contacted, and if they were willing to participate in the study and did not meet any of the exclusion criteria, they were booked for densitometry. At the time of their densitometry, some patients were asked questions about their health (Screening questionnaire – See Table 33 for study factors, and Appendix 3 for the original questionnaire). The data from this questionnaire have been analysed in a multivariate logistic regression to determine risk factors for predicting which people have low age- and gender-matched BMD (Z<-1.5). People who had low BMD (either low age- and gender-matched BMD (Z<-1.5) or low BMD compared to young adults (T<-2.5)), were eligible to participate in a randomised controlled trial of daily alendronate (10mg) versus placebo, with calcium supplements for one year. The randomised controlled trial will not be discussed as part of this thesis.

The data collected using the screening questionnaire was used to test hypothesis 1:

Hypothesis 1:

Patients with "low" (Z<-1.5) or "not low" (Z>-1.5) BMD (matched for age and gender) at either total femur or neck of femur or lumbar spine differ significantly for one or more risk factors for low bone density using an χ^2 test for categorical variables, or logistic regression for continuous variables.

This hypothesis investigates Aim 1, which is:

"To investigate whether suggested risk factors predict low bone density in people with asthma/airways disease by studying a large cohort of "at risk" subjects

(See also Chapter 1.3 Project aims and hypotheses).

All patients completed the pre-screening questionnaire. The screening questionnaire was a composite of the baseline RCT questionnaire and the pre-screening

questionnaire, designed to gain maximum information in a limited period of time (whilst the patient was in the waiting room for densitometry). There was some overlap of patients completing the baseline RCT questionnaire and the screening questionnaire.

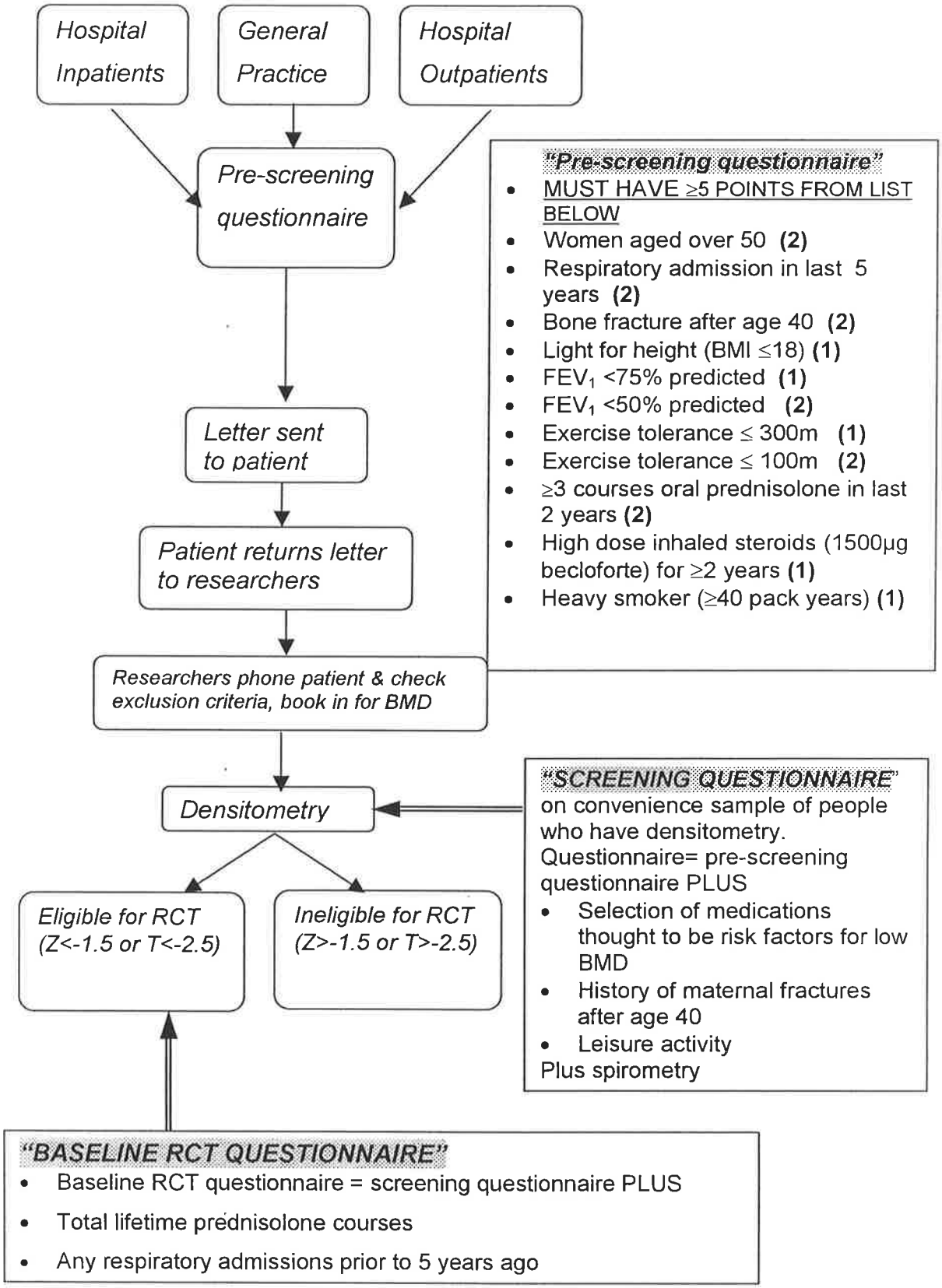


Figure 2 - Flow chart of recruiting steps in the "Osteoporosis fracture prevention trial in asthma, emphysema and chronic bronchitis"

3.2 Sampling frame

The following recruiting pools were utilised (See Figure 3):

- Respiratory outpatients (public and private) at
  - ➢The Queen Elizabeth Hospital
  - ➢Lyell McEwin Health Service
  - ➢Royal Adelaide Hospital
- Patients presenting for pulmonary function tests at the Lyell McEwin Health Service
- Inpatients discharged from the above hospitals (identified retrospectively)
- Inpatients interred in the Lyell McEwin Health Service or The Queen Elizabeth Hospital with asthma, emphysema, chronic bronchitis or COPD
- Patients participating in the Western Respiratory Health Plus Coordinated Care Trial
- Adelaide Western Division of General Practice
- Media (Messenger Press 1999; "The Pulse" 1999, 2000; Radio 5DN and 5AN)

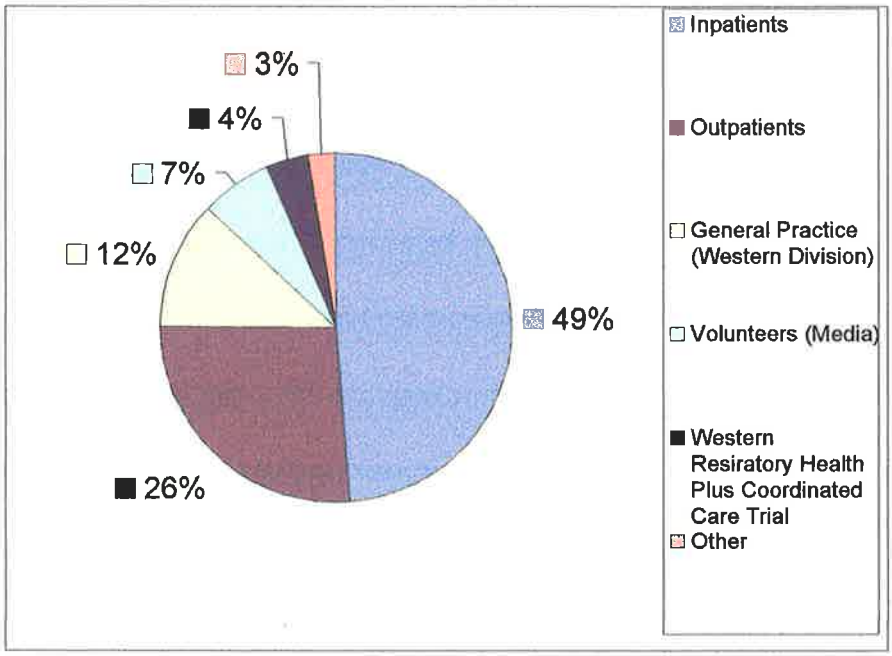


Figure 3 - Summary of patient recruiting sources

Recruiting through these sources took two general paths:

3.2.1 Outpatients:

Over 1999-2000 potential participants' hospital case notes read to ascertain study eligibility, completed pre-screening questionnaire if patient considered eligible

Clinicians discussed study with patients at outpatient consultation, and indicated patient willingness to participate to study researchers. Patients who were still eligible and willing were phoned regarding study, then booked for densitometry.

3.2.2 Inpatients:

3.2.2.1 Retrospective inpatients (IT run)

Information obtained from central hospital databases regarding patients discharged over 1997-2001 with nominated ICD-9 and ICD-10 codes for chronic bronchitis, emphysema, chronic airway obstruction, respiratory failure, and asthma.

ICD-9 codes

491.1 Mucopurual chronic bronchitis

491.20 Obstructive chronic bronchitis without mention of acute exacerbation

497.21	Obstructive chronic bronchitis with acute exacerbation
491.8	Other chronic bronchitis
491.9	Unspecified chronic bronchitis
492.8	Other emphysema
496	Chronic airway obstruction, not elsewhere classified
490	Bronchitis, not specified as acute or chronic
518.81	Respiratory failure
493.00	Extrinsic asthma without status asthmaticus
493.01	Extrinsic asthma with status asthmaticus
493.10	Intrinsic asthma without status asthmaticus
493.11	Intrinsic asthma with status asthmaticus
493.20	COAD/asthma without status asthmaticus
493.21	COAD/asthma with status asthmaticus
493.90	Standard asthma without status asthmaticus
493.91	Standard asthma with status asthmaticus

ICD-10 codes

J40	Bronchitis, not specified as acute or chronic
J41.0	Simple chronic bronchitis
J41.1	Mucopurulent chronic bronchitis
J42	Unspecified chronic bronchitis
J43.8	Other emphysema
J43.9	Emphysema, unspecified
J44.0	COPD with acute lower respiratory infection
J44.1	COPD with acute exacerbation, unspecified
J44.8	Other specified COPD
J44.9	Chronic airways obstruction, not elsewhere classified

J45.1	Intrinsic asthma without status asthmaticus
J45.9	Standard asthma without status asthmaticus
J46	Status asthmaticus
J69.9	Respiratory failure unspecified.
J96.0	Acute respiratory failure
J96.1	Chronic respiratory failure
J96.9	Respiratory failure, unspecified

Details of potentially suitable patients obtained from information technology lists of patients who discharged from each hospital over a given time frame (ranging from 1997 to present) with any of the above ICD codes as the primary diagnosis. Hospital case notes were read to ascertain study eligibility, and a pre-screening questionnaire was completed if the patient was considered suitable for the study. Potential participants' were sent a letter signed by the admitting consultant inviting them to have a BMD test.

Letters were sent in accordance with the approach listed in Phase 1 or Phase 2 (see below). Recruiting was altered from Phase 1 style to Phase 2 style to allow more streamlined recruiting based on the patient response achieved.

Phase 1: One letter was sent, and if no response was received, potential recruits received a follow up phone call from the doctor's staff inviting them to have a BMD test.

Phase 2: One letter was sent, and if no response was received, a photocopy of the original letter was sent. If no response was received, no further action was taken.

Patients responded by returning consent slips sent with the original letters or contacted us by telephone indicating whether they were willing to participate. Patients were booked for BMD tests if this was appropriate.

Patients presenting for *pulmonary function tests* had notes read as for outpatients, and then had letters as for inpatients.

Recruiting began at each hospital at different times (first at The Queen Elizabeth Hospital, then the Lyell McEwin Health Service, and finally the Royal Adelaide Hospital). More patients were in the earlier stages of recruiting at the Royal Adelaide

Hospital than at the other two hospitals. The numbers in the flow charts reflect this, with fewer people having undergone densitometry responses received from fewer people at the Royal Adelaide Hospital compared to the other two hospitals. A large proportion of patients from all three hospitals was not interested in the study (15-28%).

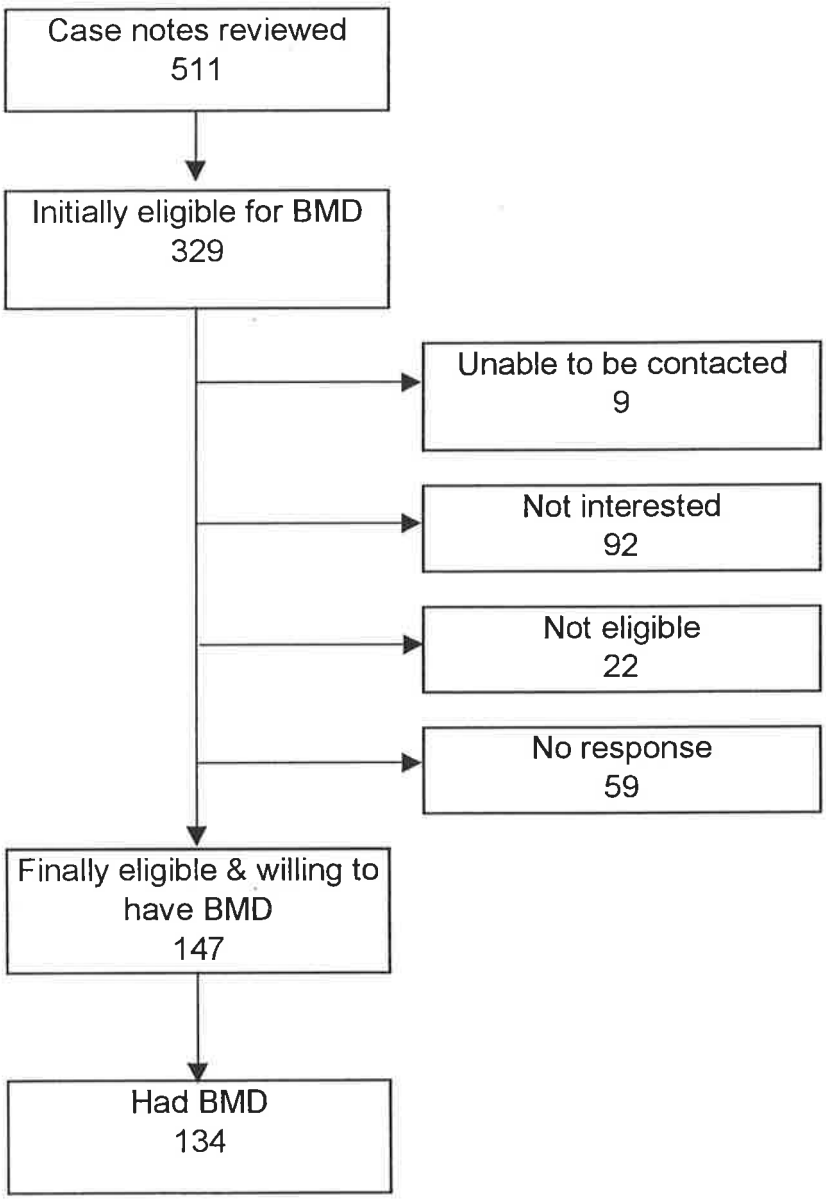


Figure 4 – Flow chart of recruiting at The Queen Elizabeth Hospital as at 24 January 2001

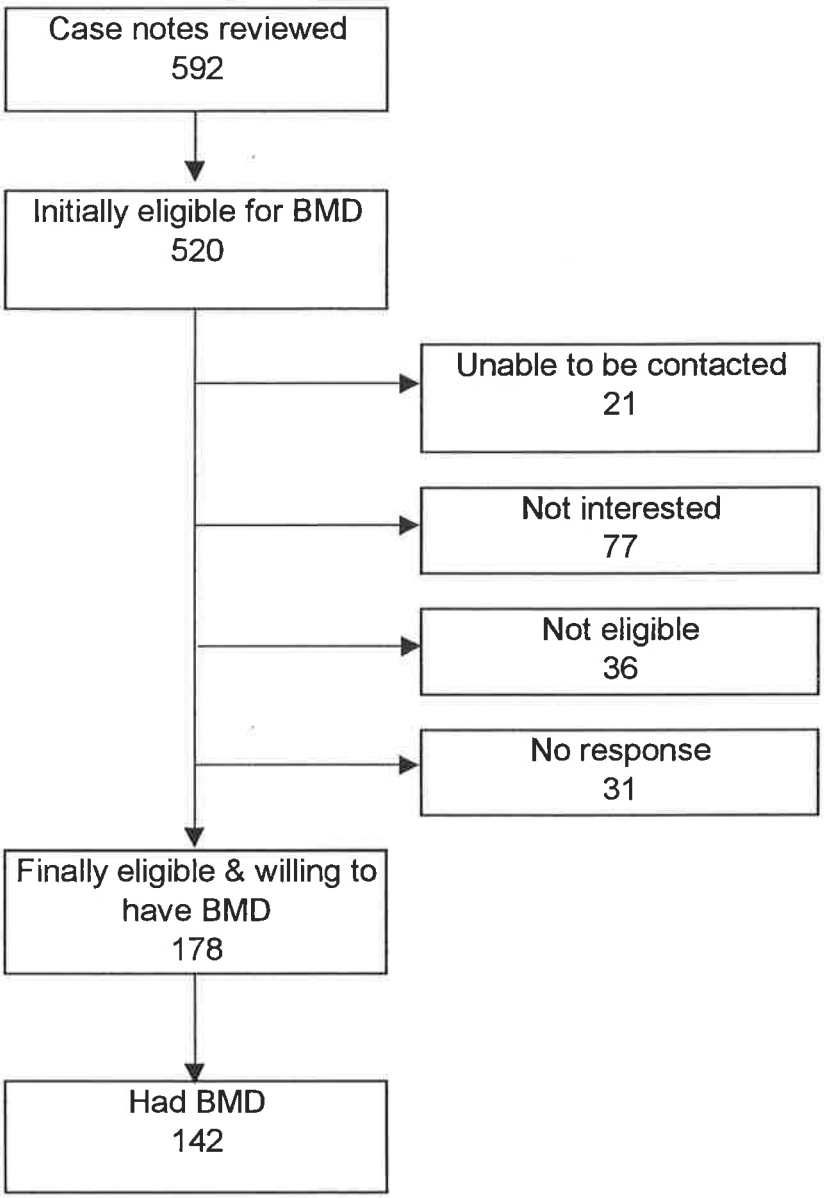


Figure 5 - Flow chart of recruiting at The Lyell McEwin Health Service as at 24 January 2001

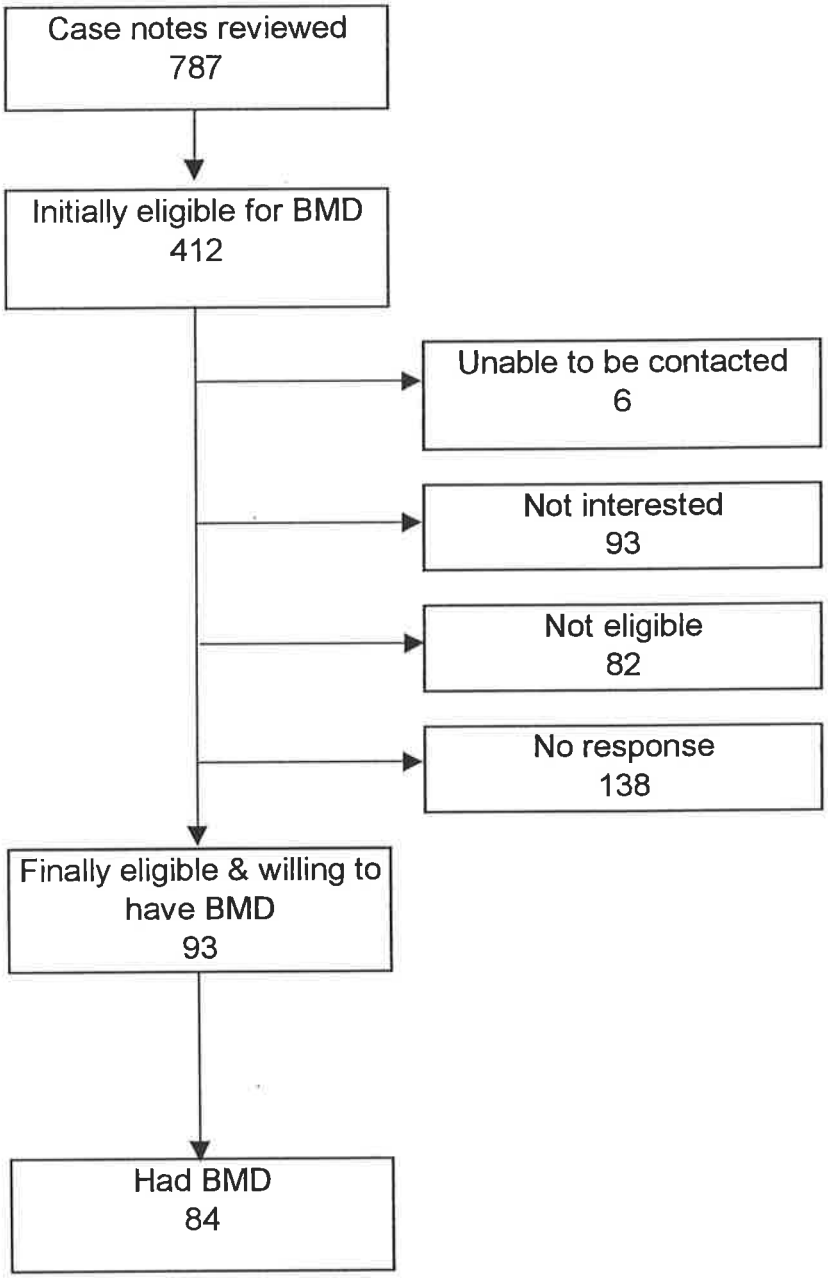


Figure 6 - Flow chart of recruiting at The Royal Adelaide Hospital as at 24 January 2001

3.2.2.1 Current inpatients

Notes were read on site at wards at The Queen Elizabeth Hospital and the Lyell McEwin Health Service and then had letters sent to them as for retrospective inpatients.

Participants in the *Western Respiratory Health Plus Coordinated Care Trial* were recruited in 1999 in a similar manner to *retrospective inpatients* except that only one letter was sent out and patients who did not respond were not followed up due to ethics restrictions.

Patients recruited through the *Western Division of General Practice* were recruited through computerised lists generated by eleven General Practitioners in the Adelaide Western Division of General Practice in 2000. Patients who indicated interest in the study were then contacted in a similar manner to *retrospective inpatients* with letters signed by individual GP's. No follow-up calls were made if patients did not respond to letters.

Patients recruited through *media* were volunteers who contacted us following media coverage of the study. If they were suitable we booked them in for a BMD test.

3.2.3 Generalisability of results

Comparisons between the patients whose screening questionnaires are presented as part of this thesis, and non-responders are presented below. This is equivalent to the "not interested" and "no response" arms of Figure 4 to Figure 6 on pages 79-81, and excludes those who we had not yet contacted about the study, and those who had missing data for age or gender.

Table 29 – Age and gender of participants completing screening questionnaire compared to "non-responders"

	Age		Proportion of participants	
	Males	Females	Males	Females
Screening questionnaire participants	67±8	64±9	100 (42%)	139 (58%)
"Non-responders"	68±8	64±10	161 (44%)	202 (55%)
One sample t-test	p=0.0725	p=0.44		
Binary test of proportions			P=0.36	

Table 30 – Recruiting source of participants and "non-responders"

			Participants
	N=	% of non	
Inpatients	254	70%	49%
Outpatients	90	25%	26%
General Practice	11	3%	12%
Volunteers (media)	1	0.3%	7%
Western Respiratory Health Plus Coordinated Care Trial	0	0.0%	4%
Other	7	2%	3%
	363	100%	100%

Table 31 – Reasons for non-participation, as supplied by "non-responders"

Reason for refusal	N=	Reason supplied (%)	Total (%)
not interested	171	73%	47%
too sick	36	15%	10%
too far to travel	21	9%	6%
other	4	2%	1%
No reason given or no reply	131		36%
Total	363	100%	100%

From the above data, it appears that study participants and "non-responders" are not significantly different in ages or in proportions of men to women (Table 30). Of those not participating, more were inpatients, and fewer were from general practice (Table 30). Most of the people citing a reason for non-participation said they were not interested or too sick to participate, although nearly a third of non-responders either did not cite a reason or did not reply to our letters (Table 31). Therefore, people who completed the study questionnaire were representative of the overall population in terms of age and gender, but were potentially less sick and therefore lower risk than the group we targeted overall.

3.3 Inclusion criteria for screening DXA

Men and women with asthma, emphysema, COPD or chronic bronchitis were eligible to participate. Different types of airways obstruction were not separated, due to well-documented difficulties in distinguishing between different types of breathing deficits in epidemiological studies.[199] FEV_1 was used in preference to any attempt to categorise by lung diagnosis (or misdiagnosis) by either physician or patient, as it is

more objective and provides more relevant information on lung function in any given subject.[200]

The age range of study participants was limited to 45-80 to enable future cost-effectiveness studies on this study population. Patients aged under the lower age limit (45 years) were considered to be a low risk population for low bone density, based on literature evidence suggesting that treatment needs to be targeted to higher risk populations to maximise cost-effectiveness.[201] Patients over the upper limit (80 years) were excluded as a high mortality rate was expected in this group, related both to advancing age and presence of respiratory disease.[202]

Patients needed to score 5 or more on our "pre-screening questionnaire" (See Table 32 and Figure 2) of risk factors for low BMD to be eligible for our study. This enabled us to select a sample of people who had a medium to high risk of having low bone density compared to the general population. Heterogeneity exists within the sample, and this is vital to allow us to find factors that effectively differentiate between patients at high and low risk of having low bone density.

Risk factors and associated weights were chosen from the literature.[4,71,65,88,99,70,200]

Chosen risk factors are listed below and also on the flow chart listed in Figure 2. The questionnaire layout used in the study is in Appendix 2 – Pre-screening questionnaire.

Table 32 – Pre-screening questionnaire

Risk factor	Associated weighting
• Women aged over 50	2
• Respiratory admission in last 5 years	2
• Bone fracture after age 40	2
• Light for height (BMI <18)	1
• FEV_1	
- low (<75%)	1
- very low (<75%)	2
• Exercise tolerance	
- limited (able to walk <300m unaided)	1
- very limited (able to walk < 100m unaided)	2
• ≥3 courses of prednisolone in the last 2 years	2
• High doses of inhaled corticosteroids (>1.5 mg beclomethasone or equivalent) daily for at least 2 years	1
• Have smoked for ≥40 pack years	1

3.4 Exclusion criteria for patients to have screening DXA

3.4.1 Contraindications for completing BMD test

- Unable to lie on BMD table

3.4.2 Contraindications for alendronate treatment
(Developed from the MIMS annual[203])

- Unable to sit upright for 30 mins or more
- Not be pregnant or likely to become pregnant for 12 months
- Moderate to severe renal impairment
- Symptomatic oesophageal reflux
- Active gastritis or ulcers of stomach or oesophagus, or oesophageal achalasia, dysphagia, oesophageal stricture
- Taking Losec, Somac or Zoton for gastro-oesophageal reflux
- Ever diagnosed with Paget's disease

3.4.3 Contraindications for randomised controlled trial

- Previously taken alendronate or etidronate
- Inability to give informed consent
- Life expectancy not exceeding 2 years

3.4.4 Contraindications for further cost-effectiveness analyses

- Bilateral hip replacements

3.5 Sampling frame for patients receiving screening questionnaire

The patients who were interviewed were a convenience sample of patients presenting for densitometry. We interviewed patients attending every second or third weekly densitometry clinic from 19/6/1999 to 4/5/2000 and then every patient where possible from 10/5/2000 to 24/01/2001. Overall, the sample included 239 patients with bone density tests dating from 19 June 1999 to 24 January 2001.

3.6 Screening questionnaire study factors

The questions asked as part of the investigation of Hypothesis 1 are listed in Table 33, and in their context on the original questionnaire in Appendix 3 – Screening questionnaire.

The screening questionnaire was a composite of the baseline RCT questionnaire and the pre-screening questionnaire (See Figure 2), and was designed to gain maximum information in the limited period of time that patients were waiting for densitometry. There was some overlap of patients completing the baseline RCT questionnaire and the screening questionnaire, but there were many patients who completed a screening questionnaire who had normal bone density who were not eligible for the randomised controlled trial of alendronate.

Table 33 – Study factors for screening questionnaire (see flow chart in Figure 2)

No.	General risk factor	No.	Respiratory specific risk factors
1	Age (years)	20	Courses of OCS in last 2 years - any/none
2	Menopausal status	21	Number of OCS courses in last 2 years
3	Age at menopause	22	Number of OCS courses (categories)
4	Gender	23	Respiratory admissions (number)
5	Height (cm)	24	Exercise tolerance
6	Weight (kg)	25	Baecke Leisure score
7	BMI	26	FEV_1 (divided into groups)
8	Ever smoked		
9	Pack years		
10	Maternal fractures		
11	Fractures since age 40 (by site)		
	Current use:		Current use:
12	HRT	27	Theophylline
13	Calcitriol	28	Daily use of inhaled corticosteroids (ICS)
14	Warfarin	29	Daily ICS dose (raw dose)
15	Calcium use	30	Daily ICS dose (categories of doses)
16	Thyroxine	31	Daily use of oral corticosteroids
17	Anticonvulsants		
	Ever use:		
18	Loop diuretics		
19	Thiazide diuretics		

3.7 Methodology of measurement of study factors

3.7.1 Introduction

Responses to study factors 1 to 4, 8-25 and 27-31 were determined from a questionnaire-based interview of the patient plus individual spirometry (Study factor 26). No attempt was made to objectively verify patient information eg medication dosage or name, patient compliance of medications etc. This was because the purpose of this study was to develop a screening tool for use by clinicians to aid in identifying patients who would benefit from bone densitometry rather than quantifying the exact nature of relationships between bone density and epidemiological risk factors for low bone density.

Study factors 5-7 consisted of data routinely collected by the bone density operator.

The interview was conducted primarily at the time of the bone density test. Results from questionnaire-based interviews from the first visit for the randomised controlled trial were also utilised provided the time of the bone density test was within the time window described in the sampling frame (Section 2.2), and there was not more than 12 weeks between bone density test and interview. Additional patients who had completed a bone density test during the time window described in the sampling frame were interviewed up to 6 months following the bone density test. Follow-up telephone calls were made to participants if any missing data was identified during the data entry phase of the study.

Further discussion of the methodology of measuring study factors 5-7, 9-19, 24-26, and 28-31 is as follows:

3.7.2 Study factors 5-7 – height, weight, and body mass index

Standing height was measured without shoes, and weight was calculated with the subject wearing regular outdoor clothes. The bone density operator used the same equipment to measure each patient's height and weight.

Body mass index (BMI) was calculated using Quetelet's index:[116]

$$\text{BMI} = \frac{\text{Weight (kg)}}{[\text{Height(m)}]^2}.$$

Quetelet's index is a reliable and valid indicator of obesity that was developed in a hospital obesity outpatient clinic, and is widely used as an indicator of obesity.

The categories developed by Garrow & Webster, 1985[116] were used for normal weight and obesity. "Underweight" is classified as <18.5.[204] However, in our actual analysis we used a more conservative cutoff for "underweight" of <20 g/cm^2 which we obtained from receiver operator characteristic curves in the multivariate analysis (See Chapter 4.6.6 on page 117 and Table 34).

Table 34 – Number of participants in BMI groups

BMI	Label	Number of patients in our sample with this BMI (N=239)	
<18.5	"underweight"	14	5.80%
18.5-25	"normal"	76	31.80%
25-30	"overweight"	81	33.90%
30-40	"obese"	62	25.90%
>40	"very obese"	6	2.50%

3.7.3 Study factors 9 - cigarette consumption (amount and duration) in "pack years"

Cigarette consumption was calculated using "pack years". It was assumed that 20 cigarettes equalled one pack. This was calculated as follows:

Pack years = (Number of cigarettes smoked per day/20) x Number of years smoked

Pack years has been used by other authors to assess smoking consumption,[97] and we consider this technique to be more informative than using "current", "former" or "ever" smoked.[60,74,205,88,72,66,65,62]

3.7.4 Study factor 10 - Maternal fractures

"Maternal fractures" was defined as any fracture the participants' mother sustained after age 40 obtained under any circumstance. Responses were coded as "yes" or "no" or "don't know". Participants were encouraged to answer "no" if they did not recall any fractures in their mother after age 40 rather than list responses as "Don't know". These were reserved for instances in which participants genuinely could not or did not know whether their mother sustained a fracture after age 40, such as if patients were adopted and did not know their birth family.

3.7.5 Study factor 11 – Fractures since age 40

The site at which the fracture occurred was recorded, as reported by the patient. Fractures at up to two sites were recorded and only one fracture at each site was included.

3.7.6 Study factors 12-17 and 28-31 – Current medications

Participants were asked to bring a list of current medications as a memory aid. Use of listed medications was recorded and for analysis purposes was collected as a binary yes/no variable (without taking into account daily dosage).

3.7.7 Study factors 18-19 – Ever use of diuretics

Diuretics were separated into two categories – "loop" eg frusemide and "thiazides" eg hydrene. These types of diuretics are known to have different effects on bone density. Low dose hydrochlorothiazides have been shown to preserve BMD even in normotensive adults.[206] Ever use of loop and thiazide diuretics was determined from patient recall of any diuretics ("fluid tablets") ever regularly prescribed for the patient in question. Reasonable efforts were made to determine the identity of tablets where the patient was unsure by cross-referencing with MIMS[203] for tablet colour, shape, or recalled fragment of drug name.

3.7.8 Study factor 20-22 – Number of courses of oral corticosteroids in the last 2 years

When the number of courses of oral corticosteroids taken in the last two years was transformed into categorical data, the categories used were: 0; 1-4; 5-8; >9 courses.

We only asked about corticosteroid usage in the last two years. Therefore, if participants have changed their OCS usage over time, this will be missed. This could be important, as bone loss occurs most when use of corticosteroids in high doses begins.[207] However, collecting more detailed information about past corticosteroid intake does not predict low BMD,[208] and therefore we have elected to ask about booster courses of OCS in the last two years only.

3.7.9 Study factor 24 – Exercise tolerance

Three levels of exercise tolerance (unaided on a flat surface) were created using this variable – either ≤100 m, 100-300m, or >300m. This was estimated by the participant and was not externally validated.

3.7.10 Study factor 25 – Baecke Leisure Score

The questionnaire by Baecke *et al.*[209] was considered suitable for measuring activity in leisure time in this study. It is reliable, as assessed by good test-retest correlations of 0.74 for leisure-time activity in the original study;[209] and has previously been used in a cross-sectional study of community dwelling asthmatics which investigated the

association of beclomethasone dipropionate and other lifestyle factors with bone density eg physical activity.[200]

Leisure score was calculated from non-sport leisure questions as per Baecke *et al.*[209] and referred to current activity only (last 5 years). Non-sport leisure questions were chosen above the other indices in Baecke *et al.*[209] (occupational activity and sport leisure index) as non-sport leisure had the highest association with bone density in the cross sectional study mentioned above.[200]

Slight modifications were made to the original non-sport leisure questions for use in this study.

In asking the questions we changed the subject of the sentences because we were administering the questionnaire to patients rather than them completing the questionnaire themselves, eg:

"During leisure time *I* walk"

to

"During leisure time *do you* walk?"

We changed the wording in the questions:

"During leisure time I *cycle*"

and

"How many minutes do you walk and/or *cycle* per day to and from work, school and shopping"

to

"During leisure time do you *ride a bike*"

and also

"How many minutes did you walk and/or *ride a bike* per day to and from work, or shopping".

This was done to reflect Australian wordings for the action of bicycle riding.

We asked one question about sport activity in leisure time "During leisure time do you play sport". We did not use this question in the analysis as the heterogeneity of responses was limited, with 80% of respondents saying they never played sport in leisure time.

We also omitted references to "school" in the question "How many minutes do you walk and/or ride a bike to and from work, school and shopping". Our cohort had mean age of 65±8 years (older than the Dutch cohort on which the original study was based in which participants' ranged from 19-31). Therefore the vast majority of our subjects were middle aged or elderly people who were too old to attend school.

Some may question whether the reliability and validity of the Baecke instrument can be appropriately extrapolated to this study since our study population is significantly older than the original Dutch cohort in which the Baecke questionnaire was developed. Our cohort is also older than the study of community-dwelling asthmatics where the average age of respondents is 45±14 years (110 female and 63 male), compared to 65±7 for our study (139 women, 100 men). The advantage of the Baecke questionnaire is that it has three indices that can be used separately. The work, and particularly the sport index have limited relevance to this population, and in the previous study of asthmatics they were not significantly associated with low BMD.[208] The non-sport leisure index included regular activities which should not be limited by age per se, such as watching TV or walking, and as the questionnaire was very short and therefore had the advantage of limited respondent burden.

3.7.11 Study factor 26 – FEV_1

Lung function was measured objectively using FEV_1 (forced expiratory volume in one second), standardised to percent predicted for a patients age, gender and height. The algorithms used for the study were the E.C.C.S[210] which were pre-programmed into the MicroLab 3300 spirometer used for the study (Micro Medical Ltd, Kent, England). The MicroLab 3300 complies with the American Thoracic Society recommendations for spirometer in terms of accuracy (±3%), manner of test procedure (best of 3 reproducible tests with patient in a seated position),[211] except nose pegs were not used.

FEV_1 was preferred over other methods of assessing breathing restriction eg forced vital capacity as FEV_1 is the best measure of disease stage and symptom severity.[212] The same spirometer was used in 222/239 study participants. The remaining 17 people did not have spirometry tests done at the same time as the questionnaire. Their FEV_1 scores were obtained from a variety of sources, and were not administered by staff in our research team. These sources included The Queen Elizabeth Hospital pulmonary function laboratory, and also various spirometry

devices in outpatients at The Queen Elizabeth Hospital, the Lyell McEwin Health Service, or the Royal Adelaide Hospital as recorded in the patient's hospital case notes. FEV_1 values were only accepted for use in this analysis if the sourced values were within ±6 months of the screening questionnaire to minimise any change in the lung function of study participants due to a change in the severity of their underlying lung disease. The reproducibility of FEV_1 data obtained from spirometers in hospital outpatient departments is unknown, and may not comply with ATS recommendations.

We expect that some inter-operator variation will have been present, as there were 5 spirometry operators as part of our research team, and numerous others not part of our team (who performed the 17 tests we were able to obtain from other sources). Whilst one investigator (myself, LL) trained the other four operators who were part of our team, and observed their technique whilst they were first learning, to ensure that our techniques were as similar as possible, we did not statistically analyse the spirometry by operator to assess if there were any systematic differences in FEV_1 by operator. However, in the final statistical analysis, we used FEV_1 only as a categorical rather than continuous variable, and therefore the FEV_1 data would have to have been misclassified in order to affect the final results.

3.7.12 Study factor 28-30 – Inhaled corticosteroids

Daily dose of inhaled corticosteroids was recorded, and determined from dosage per puff from metered dose inhalers and prescribed number of inhalations per day. When the dose of inhaled corticosteroid was transformed into categorical data, the categories used were 0; <1000 μg; <2000 μg; >2000 μg. As seen in Table 35, of the 80% of our population taking inhaled corticosteroids, nearly half were taking FP (46%), a third BDP (30%), and the remaining quarter BUD (23%).

Table 35 – Inhaled corticosteroid usage by name in our population

Name of inhaled corticosteroid	Usage
Beclomethasone dipriopionate (BDP)	58 (30%)
Budesonide (BUD)	23 (23%)
Fluticasone propionate (FP)	89 (46%)
	192 (100%)

*80% of patients used inhaled corticosteroids (192/239)

Different ICS are known to have different effects – both in terms of altering respiratory function (as measured by FEV_1 or peak flow), and also in terms of

systemic effects, such as suppression of bone turnover or adrenal-cortical function. The following comparisons are available from the literature.

In terms of clinical efficacy, FP is twice as potent as BUD in changing morning peak flow,[213] and is also more potent than BDP, although there is insufficient evidence to determine the potency ratio.[214]

In terms of systemic effects, BDP is twice as potent as BUD in suppressing adreno-cortical function,[215] but there is insufficient evidence to decide if there are differences in the systemic effects of FP and BDP.[214] There are differences not only between different ICS, and also the method of delivery, with the FP Diskhaler more potent than BUD Turbuhaler with a potency ratio of 1.7:1.0.[216] The potency ratio between FP and BUD measured dose inhalers is 3:1[214] and the potency ratio between FP & BUD dry powder inhalers is 1.5:1 in adults. There is inadequate information to calculate an accurate systemic effect ratio for BDP measured dose inhalers versus BUD or FP.[214]

Therefore, we can conclude that the effects of ICS on the body vary both by ICS type and dose, and by method of delivery eg measured dose inhaler versus dry powder inhaler, and also by numerous other factors, such as spacer usage.[214] We did not record the method of delivery or duration of use of the current or previous ICS, and thus would have been unable to correctly calculate any potency ratios to give different weighting to individual ICS. Also, many patients would have used other types of ICS or different methods of delivery over the course of their disease, and so to calculate any potency ratios accurately we would have needed to take these into account also – leading to an immensely complex potency ratio which would be of limited applicability to clinical practice.

Therefore, we have pooled all three ICS types used by our study subjects (FP, BUD and BDP) for use in study factors 23-30.

3.8 Outcome factors

3.8.1 Bone density measurement by DXA

Bone density was measured by a DXA (dual X-ray absorptiometry) using a Lunar DPX_{plus} machine (Lunar Radiation, Madison, WI, U.S.A.) by trained bone density technicians using the recommended methods of operations.[217] Scans were analysed using Lunar DPX-IQ version 4.6b software and were undertaken at The Queen

Elizabeth Hospital Department of Endocrinology. Daily quality assurance tests and weekly scans of aluminium spine phantoms as supplied by the manufacturer were performed to monitor system bias and precision. During a 51 week period in 2000, the average of 51 weekly measurements from the densitometer used for our study (using the Lunar spine phantom) gave a mean value of 1249.4±4.6 mg/cm^2.[218] This standard deviation represents 0.36% of the mean value. No reference standard is currently available for DXA.

3.8.2 Bone density sites

Bone density values at the lumbar spine (L2-L4),[219] total femur, and neck of femur[220] were used. Bone density was standardised for age, race and gender to *Z*-scores. *Z*-scores were then categorised as low (*Z*<-1.5) or not low (*Z*>-1.5) bone density at any one of the three sites measured. If low bone density could not be accurately assessed at a particular site for any reason, patients were allocated to either the "low" (*Z*<-1.5) or "not low" (*Z*>-1.5) bone density groups based on the available data at other sites. Fractures are best predicted by site-specific measurements,[14] In addition, hip BMD does predict "all" fractures a little better than spine BMD (RR of 1.6 (95% CI 1.4 – 1.8) compared to 1.5 (95% CI 1.4 – 1.7)) for 1SD decrease in BMD at this site.[14]

Risk factors for low BMD may differ between sites, reflecting the structure of the bone (cortical vs trabecular), and different types of mechanical loading on the bone, such as physical activity. Therefore, it is possible that different risk factors will predict low BMD at the spine and hip in our population. However, we have elected to pool the sites in the first instance as we were aiming for a set of risk factors that could be used as a clinical tool such as that in Figure 18 on page 182 to help physicians decide who should be sent to, or excluded from densitometry. Additional analyses by site and gender have also been provided following the analysis using data pooled by site and gender.

3.8.3 Choosing a bone density cutoff

Fracture risk increases exponentially with decreasing BMD,[15,18] and there is considerable overlap in BMD values of groups with and without fractures.[221] The WHO definition of osteoporosis[222] defines an arbitrary threshold defined primarily for epidemiological purposes which includes the majority of people with osteoporotic

fractures, and is confounded by such factors as variability between equipment, and differing reference ranges between different skeletal sites and ethic groups. Given that the WHO definition defines osteoporosis in terms of absolute risk relative to young adults, it has become regular clinical practice to use *T*-scores to decide whether to treat, with *T*<-2.5 the BMD cutoff below which treatment should begin, and *T*<-1 the BMD cutoff below which prevention of future fractures should begin.[223,224] *Z*-scores are another method of assessing BMD, and are used primarily to assess age-matched BMD, and thereby identify non age-related deficits in bone density. There is less consensus about the best cutoff to use, as different guidelines,[224] bureaucracies,[225] and authors[226] use different cutoffs (*Z* <-1, *Z* <-1.5 and *Z* <-2). There is no evidence base for the use of one cutoff over others.

We have chosen to use the cutoff of *Z*<-1.5 for further analysis.

There were two reasons for this:

1) *Z*<-1.5 is the bone density cutoff at which subsequent DXA's are subsidised by Medicare every 24 months, at no cost to the consumer.[13]

2) For pragmatic purposes, we required the best mix of low bone density with sufficient numbers to run useful analyses. There were insufficient subjects who had bone density of *Z*<-2.0 for further analysis (18/239 – 8%), whereas 20% of our sample had bone density of *Z*<-1.5 (49/239). 6.68% of the reference population have a *Z*-score of <-1.5.[10]

3.8.4 Other considerations regarding observed BMD in individual cases

Densitometry results could have been affected by unidentified crush fractures, and spinal osteophytosis, both of which artificially elevate spine BMD, potentially misclassifying the patient as non-osteoporotic. Therefore, the densitometry results of all patients were manually double-checked to identify any scans that may have contained undetected anomalies or discrepancies, and we further investigated individual cases where patients *Z*-scores at spine, neck of femur or total femur differed by two standard deviations or more (N=28).

Of these 28 patients, 4 patients had BMD *Z*-scores of ≥3 at the neck of femur, total femur, or lumbar spine. Three of these patients had accessible case-notes at either The Queen Elizabeth Hospital, Lyell McEwin Health Service, or the Royal Adelaide Hospital. Casenotes of these three patients were read to ascertain if any diagnosis

had been made which could explain their high *Z*-scores, particularly diagnoses relating to study exclusion criteria that may have been overlooked when the patient was recruited.

Following casenote inspection, no anomalies were found in two of the three patients whose case notes could be sourced. The other patient (Unique ID 777) was subsequently dropped from the analysis. His *Z*-scores were 5.61, 1.73, 2.9 for the lumbar spine, neck of femur and total femur respectively. We could find no diagnosis which would explain his high *Z*-scores, especially that of his spine, which had a *Z*-score of 5.61. We considered that such an event was unlikely to have occurred by chance ($p<0.00001$) and therefore explainable by diffuse idiopathic skeletal hyperostosis (DISH), or some other pathology unknown to us.

Spine densitometry results are routinely assessed to identify "crush" fractures (on the basis of the scan), and suspicious vertebrae are omitted from the calculation of the bone mineral density of the spine. Spinal osteophytosis is reported to affect up to 70% of the population,[227] but we were unable to assess the results or adjust for this phenomenon, as we did not take X-rays as part of this study. Overall, *Z*-scores are higher in the spine than either femur site in both sexes (Table 38), although the shape of the curve was not significantly skewed, or the mean significantly different to zero (Table 36). We would have expected BMD at the spine to be lower than the hip due to preferential thinning of trabecular bone by corticosteroids, as the spine is mostly trabecular bone whereas the hip has more cortical bone. However, despite the above, diagnoses of "low BMD" is made in more cases by spinal BMD than femoral BMD in women, with spine and femur equally good in men (See Table 37). This is contrary to what would have been expected if spinal osteophytosis was adversely affecting our results.

Conclusion

People with moderate to severe asthma, emphysema, COPD or chronic bronchitis who had attended respiratory outpatients or had been hospitalised for their airways disease at The Queen Elizabeth Hospital, the Lyell McEwin Health Service, or the Royal Adelaide Hospital over 1999-2002 were targeted for the study. In addition, patients were sourced from a number of general practices in the Adelaide Western Division of General Practice as well as a number of other sources. Patients who scored more than 5 points on our pre-screening questionnaire and satisfied other

inclusion and exclusion criteria were invited for densitometry, and completed a more detailed questionnaire on their health (screening questionnaire). This data was used to test Hypothesis 1: that patients with "low" (Z<-1.5) or "not low" (Z>-1.5) age- and gender-matched BMD at either the neck of femur, total femur or lumbar spine differed significantly for one or more risk factors for low BMD using a χ^2 test for categorical variables, or logistic regression for continuous variables.

Chapter 4 - Results of a risk factor analysis to develop a screening tool to identify patients with respiratory disease who are at increased risk of low bone density

Data collected using the screening questionnaire was analysed using logistic regression, first one factor at a time (univariate), then a number of factors together (multivariate) to generate a risk factor model to identify a high risk group for low BMD.

4.1 Analyses

This analysis relates to Hypothesis 1 (Section 1.5, page 16) which is:

That patients with "low" (Z<-1.5) or "not low" (Z>-1.5) BMD (matched for age and gender) at either total femur or neck of femur or lumbar spine differ significantly for one or more risk factors for low bone density using an χ^2 test for categorical variables, or logistic regression for continuous variables.

Analysis was performed using Stata 6.0 (Stata Corporation, USA).

4.1.1 Univariate analysis

Each risk factor was tested for association with the outcome factor using logistic regression (variables with continuous data) or χ^2 tests (variables with categorical or binary data) at the significance level of α=0.25. This approach has been used in studies that developed screening tools to identify patients with low BMD,[190] with similar α levels. Variables found to be significantly associated with low BMD at univariate level could therefore be considered to be independently associated with low BMD.

4.1.2 Multivariate analysis

Risk factors which were significantly associated with the outcome variable at univariate level were placed into a multiple stepwise regression model using forward selection at the α=0.10 level. Goodness of fit of the model was calculated using the Hosmer-Lemeshow χ^2 statistic. Sensitivity, specificity, positive predictive value, negative predictive value and area under the receiver operating characteristic (ROC) curve.[228]

were calculated at the probability level which corresponded most closely to a sensitivity of 90% (86%). The logistic model was calculated for this probability cutoff, thus generating the final screening model.

The number of patients in the final analysis was 239.

4.2 Patients with missing data at skeletal regions of interest

Seven of the 239 subjects did not have completed scans of the lumbar spine. One patient did not have completed scans of the femur.

The 7 patients who did not have spine scans had girth of ≥28cm, and were therefore unable to fit underneath the arm of the DXA machine. These seven patients were all obese, with an average weight of 116±6kg and BMI of 41± 2, compared to the average BMI for the whole population of 27±6. They had average femur *Z*-scores of 0.3±0.4 for neck of femur and 0.7±0.3 for the total femur.

The one patient who did not have a femur result had polio and was unable to be appropriately positioned for the DXA scan. His spine *Z*-score was 2.5.

In these 8 subjects low bone density could not be assessed at either the hip or spine. Therefore, these patients were allocated to either the low ($Z<-1.5$) or not low ($Z>-1.5$) bone density groups based on the available data at other sites that could be accurately assessed.

4.3 Bone density distribution of the sample

4.3.1 Shape and position of the bone density distribution of our population

As seen in Table 36, *Z*-scores for the sample of patient data studied in this research were Normally distributed – in 3 out of 3 sites in men and 2 out of 3 sites measured in women (skewed slightly to the left at the neck of femur). The mean was not significantly dissimilar to zero for women, but the bone density of the men was significantly different to zero in 2 out of 3 sites measured, with the mean BMD nearly half a standard deviation below zero at the neck of femur.

Table 36 – Normality and position of bone density distribution in our sample

	Lumbar spine		Neck of femur		Total femur	
	Women	Men	Women	Men	Women	Men
N=	134	98	139	97	139	99
"Normal" ‡	✓	✓	×	✓	✓	✓
BMD mean =0 †	✓	✓ (p=0.0512)	✓	×	✓	×
Bone density (*Z*-score)	+0.20±1.39	-0.26±1.30	-0.06±1.00	-0.47±0.86	-0.02±1.08	-0.35±1.04

‡ using the Shapiro-Wilk test for normality, using $p<0.05$
† using the one-sample t-test for x=0

Given the selection factors (Table 32 – Pre-screening questionnaire on page 84), we expected that the mean BMD would be significantly less than zero in most of the sites and both genders, whereas only one site is below zero, and this mean BMD is higher than the 1SD decrease reported in earlier studies.[229] Explanation for this discrepancy include higher risk individuals not responding or being unwilling to participate in the study (See section 3.2.3 Generalisability of results on page 82), overly generous weighting for some items, such as giving post-menopausal women two points; and including risk factors which selected more for low *T*-scores than low *Z*-scores, such as exercise tolerance. Factors such as these resulted in the women in our sample having higher BMD than the men, and younger women having lower Z-scores than older women. Another explanation is that the estimate of mean BMD of Z=-1 overestimates deficits in BMD for people with moderate to severe disease due to biases in study design such as over-sampling of higher-risk patients.

Conclusion

The bone density of women is Normally distributed at two sites, and is slightly skewed to the left at the neck of femur, and the mean is below zero for men in only

one the sites measured, and is approximately zero for men and women at the other sites measured. Bone density of the men is Normally distributed at all three sites, and the mean is significantly different to zero (lower) in two out of three sites.

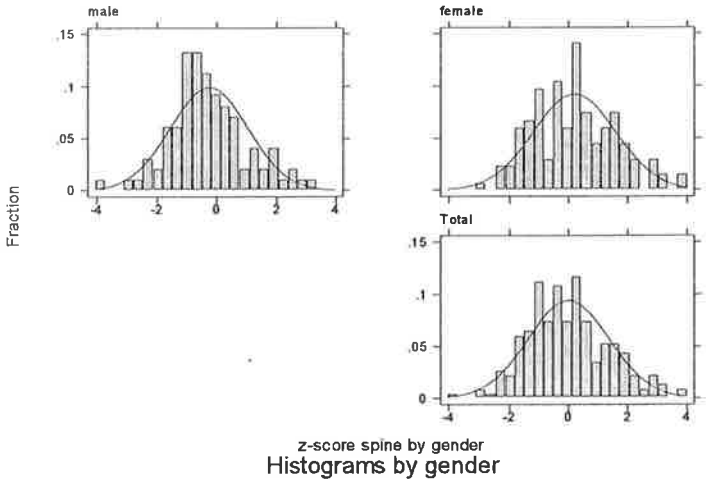


Figure 7 - Histogram of spine Z-scores, by gender

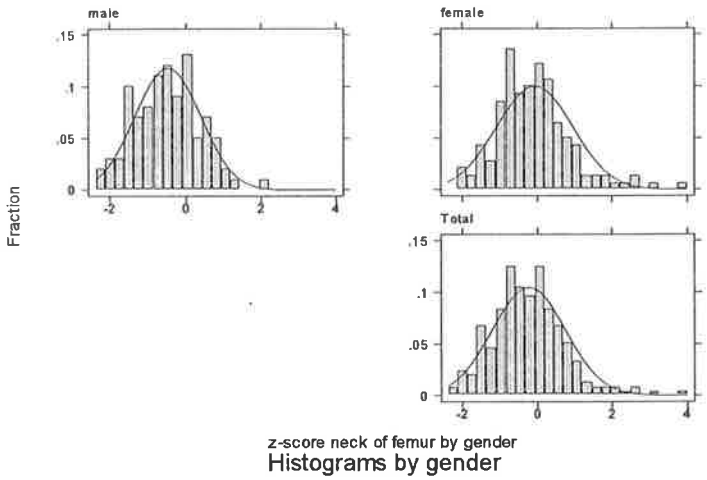


Figure 8 - Histogram of neck of femur Z-scores, by gender

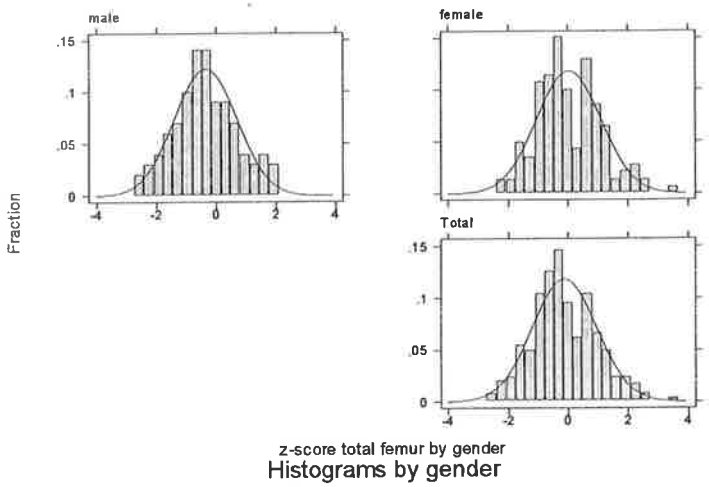


Figure 9 - Histogram of total femur Z-scores, by gender

4.3.2 Breakdown of patients with a diagnosis of low bone density by site

For the purposes of this study, we assessed whether our study patients had low BMD (Z<-1.5) at one or more of three anatomical sites (lumbar spine, neck of femur, and total femur). Some patients will have low BMD at one site only, and others at more than one site. The number of patients who have BMD below three Z-score cutoffs (Z<-1, Z<-1.5, Z<-2.0) at each anatomical site, by gender, are illustrated in the Venn diagrams in Chapter 4.3.

These diagrams concur with the finding of Phillipov *et al.*[230] - that measurement of bone density at the lumbar spine is the best site for identifying women with low bone density at the neck of femur or lumbar spine (87.1% compared to 45.1% at the neck of femur), using T<-2.5 as the definition of low bone density. In men, the lumbar spine and the neck of femur are equally useful for detecting low bone density (69.3% and 67.5% for the lumbar spine and neck of femur, respectively). While we used Z–scores, we obtained similar results.

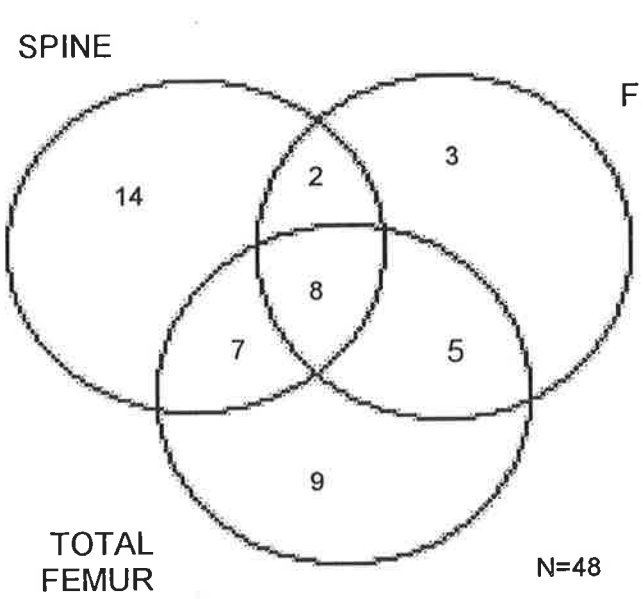
Table 37 – Skeletal site at which low BMD is identified when two or three sites are measured

	Women - measure three sites			Women - measure two sites only	
Bone density	LS (%)	NOF (%)	TF (%)	LS (%)	NOF (%)
Z<-1.0	65	37	60	79	46
Z<-1.5	65	26	66	88	35
Z<-2.0	83	16	33	83	33
	Men - measure three sites			Men - measure two sites only	
	LS (%)	NOF (%)	TF (%)	LS (%)	NOF (%)
Z<-1.0	50	65	65	58	75
Z<-1.5	53	46	57	64	55
Z<-2.0	50	33	50	66	44

LS = lumbar spine, NOF = neck of femur, TF = total femur

These findings are different to studies investigating site-specific BMD for fracture prediction, where hip BMD was slightly better at predicting all fractures than spinal BMD.[14] However, these studies provide no information on where these people have low BMD – whether hip or spine or both.

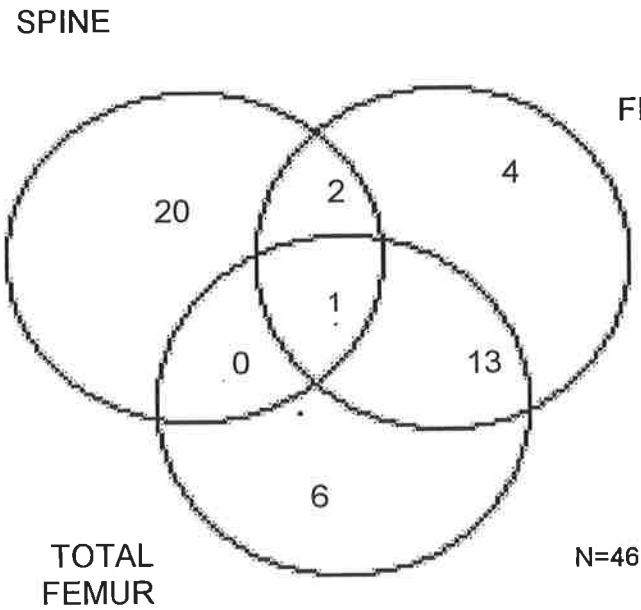
Definition of low bone density = Z<-1



Including total femur - 48 people with osteoporosis
31/48 at spine=65%
18/48 at neck of femur=37%
29/48 at total femur=60%

Excluding total femur - 39 people with osteoporosis
31/39 at spine=79%
18/39 at neck of femur=46%

Figure 10 – Diagnosis of low BMD (Z<-1.0) by site in women

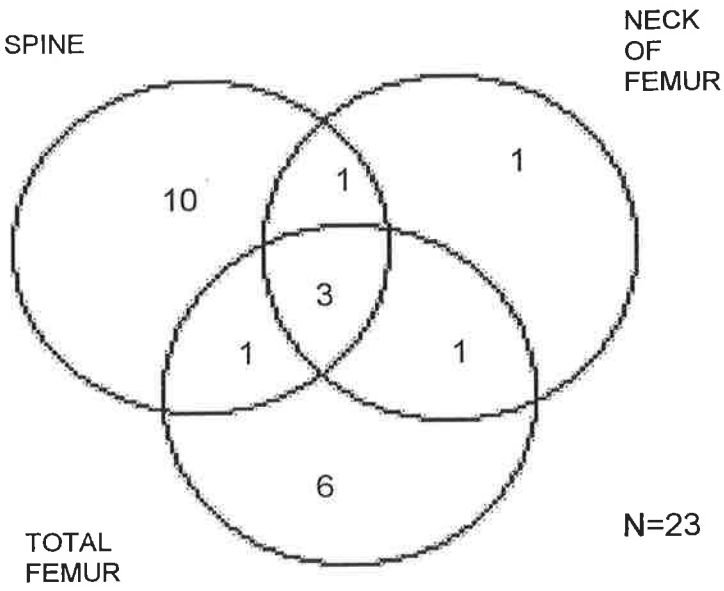


Including total femur - 46 people with osteoporosis
23/46 at spine=50%
20/46 at neck of femur=65%
20/46 at total femur=65%

Excluding total femur - 40 people with osteoporosis
13/40 at spine=58%
20/40 at neck of femur=75%

Figure 11 – Diagnosis of low BMD (Z<-1.0) by site in men

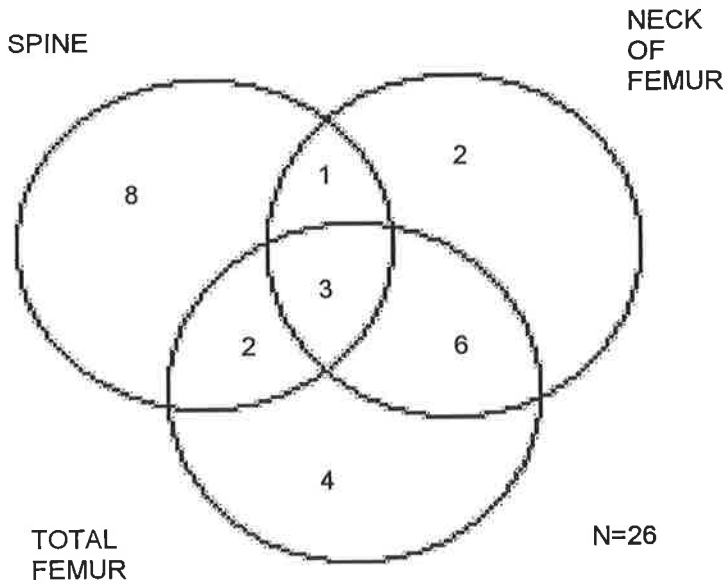
Definition of low bone density = Z<-1.5



Including total femur – 23
people with osteoporosis
15/23 at spine=65%
6/23at neck of femur=26%
11/23 at total femur=47%

Excluding total femur - 17
people with osteoporosis
15/17 at spine=88%
6/17 at neck of femur=35%

Figure 12 - Diagnosis of low BMD (Z<-1.5) by site in women

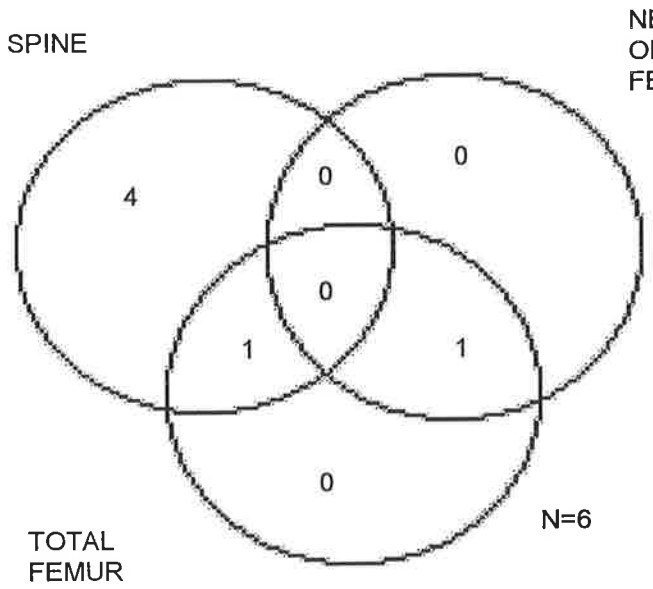


Including total femur –26
people with osteoporosis
14/26 at spine=53%
12/26 at neck of femur=46%
15/26 at total femur=57%

Excluding total femur – 22
with osteoporosis
14/22 at spine=64%
12/22 at neck of femur=55%

Figure 13 - Diagnosis of low BMD (Z<-1.5) by site in men

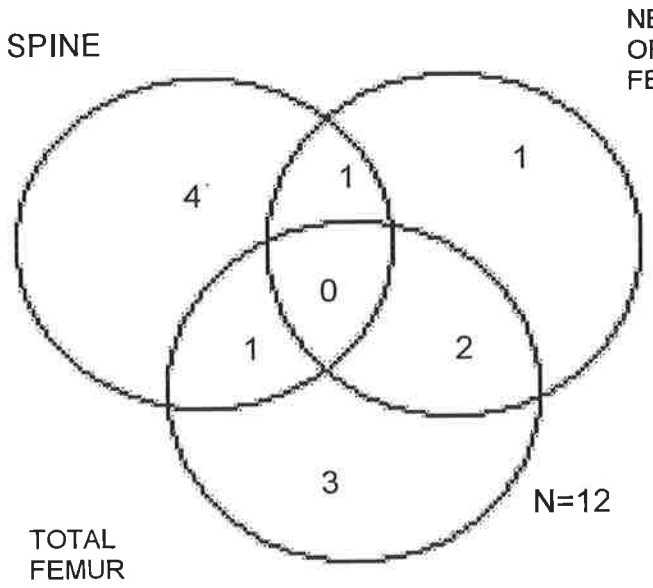
Definition of low bone density = Z<-2.0



Including total femur – 6
people with osteoporosis
5/6 at spine=83%
1/6 at neck of femur=16%
2/6 at total femur=0%

Excluding total femur – 6
people with osteoporosis
(as above)

Figure 14 - Diagnosis of low BMD (Z<-2.0) by site in women



Including total femur –12
people with osteoporosis
6/12 at spine=50%
4/12 at neck of femur=33%
6/12 at total femur=50%

Excluding total femur – 22
people with osteoporosis
6/9 at spine=66%
4/9 at neck of femur=44%

Figure 15 - Diagnosis of low BMD (Z<-2.0) by site in men

4.4 Baseline characteristics of study population

The baseline characteristics of our study population are listed in Table 38.

4.4.1 Comparison to "normal" populations[§]

Our sample is middle aged, with more women than men ($p<0.05$), with similar BMD to reference populations when matched for age and gender in the women, but lower BMD in men (spine $p=0.05$, neck of femur $p\leq0.0001$, total femur $p\leq0.01$), compared to reference populations.[10] Both men and women were overweight for their height ($p\leq0.0001$)[116] and sedentary in their leisure time ($p\leq0.001$)[209] compared to reference populations.

4.4.2 Comparisons between men and women

Men and women had different patterns of risk factors. We considered this to be an artefact of the pre-screening questionnaire (See Table 32 on page 84, and Appendix 2), where men needed more risk factors to be eligible for the study. Men had lower age- and gender-standardised BMD at the spine ($p\leq0.05$), neck of femur ($p<0.01$) and total femur ($p\leq0.01$) than women. Men had poorer lung function (as measured by FEV_1 % predicted) than women ($p\leq0.001$), and different underlying respiratory illnesses. More women were asthmatics ($p\leq0.001$), and more men had emphysema ($p\leq0.001$). No difference was found in the proportion of men and women with COPD and chronic bronchitis (Note: respiratory illness was self-reported, and respondents could choose more than one underlying illness). There were no significant differences in the proportion of men and women taking daily oral corticosteroids, theophylline, loop diuretics, calcitriol, warfarin, or daily dose of inhaled corticosteroids. There were more women than men taking hormone replacement therapy ($p\leq0.001$), calcium supplements ($p\leq0.05$), ever having used thiazide diuretics ($p\leq0.01$), or daily thyroxine ($p\leq0.01$). Women were shorter ($p\leq0.001$) but heavier ($p\leq0.01$), and had higher body mass index ($p\leq0.05$) than men. More men had ever smoked cigarettes ($p\leq0.0001$), and men had higher overall cigarette consumption (in pack years) ($p\leq0.0001$) than women.

[§] All comparisons in this section are one-sample t-tests

Table 38 – Baseline characteristics of study population

	Male (mean ± SD)	Female (mean ± SD)	Total
Age	67±8 (49-80)	64±9 (45-80)	65±7 (45-80)
Gender	N=100 (42%)	N=139 (58%)	N=239
Lumber spine BMD (mg/cm^2)	1126±174 (N=98)	1039±209 (N=134)	
Neck of femur BMD (mg/cm^2)	855±140 (N=99)	827±155 (N=139)	
Z-score -lumbar spine	-0.26±1.30	+0.20±1.39	
- neck of femur	-0.47±0.86	-0.06±1.00	
- total femur	-0.35±1.04	-0.02±1.08	
T-score - lumbar spine	-0.85±1.44	-1.24±1.67	
- neck of femur	-1.73±1.05	-1.27±1.30	
- total femur	-1.28±1.25	-1.00±1.42	
% post-menopausal	-	93%	
Proportion with BMD *Z*<-1	46%	34%	39%
Proportion with BMD *Z*<-1.5	26%	15%	21%
Proportion with BMD *Z*<-2	12%	4%	8%
Airways obstruction[†]			
Normal (>80% predicted)	7%	30%	20%
Mild obstruction (60-80%)	16%	24%	21%
Moderate obstruction (40-60%)	27%	29%	28%
Severe obstruction (<40%)	50%	18%	31%
Mean FEV_1 (% predicted)	44±19	64±25	56±25
Baecke Leisure Score‡	1.0±0.7	0.9±0.1	0.9±0.7
Height (cm)	170±6	156±6	
Weight (kg)	75±15	69±18	
Body mass index[§]	26±4	28±6	27±6
Ever smoked	98%	70%	82%
Pack years	56±44	25±27	38±38
Self-reported diagnosis			
Asthma	44%	73%	61%
COPD	26%	17%	21%
Emphysema	52%	29%	38%
Chronic bronchitis	9%	10%	10%
Current use:			
HRT	8%*	39%	26%
Calcium tablets	18%	32%	26%
Calcitriol	8%	5%	6%
Thyroxine	2%	14%	9%
Daily oral corticosteroids (OCS)	19%	14%	16%
Anticonvulsants	1%	1%	1%
Diuretics	17%	22%	20%
Theophylline	15%	9%	12%
Warfarin	5%	4%	4%
Rib fractures	10%	7%	8%
Spine fractures	2%	1.4%	1.7%
Any OCS in last 2 years	64%	70%	67%
Number of OCS courses in last 2 yrs	3.1±4.7	2.7±3.8	2.8±4.1
Current daily ICS dose (µg)	954±671	876±605	909±633
Inhaled corticosteroids (ICS)	78%	82%	80%
Beclomethasone	29%	31%	30%
Budesonide	21%	25%	23%
Fluticasone	50%	44%	46%
Ever use:			
Diuretics	23%	32%	28%
Thiazide diuretics	2%	6%	5%

[†] British Thoracic Society guidelines (FEV_1 % predicted)[231]
‡Baecke *et al.* 1982.[232] Mean activity levels 2.8±0.1 (women), 3.1±0.0 (men), p≤0.01 for our population. [§] "Normal" BMI 22.5[116], p≤0.001 for our population
* Includes use of testosterone replacement therapy

4.5 Association between low bone density and individual risk factors

We used logistic regression for testing the association between low BMD and individual risk factors, because our outcome variable (low or not low BMD) was binary.

While men and women in our study had slightly different patterns of risk factors at baseline (See Chapter 4.4 and Table 38), we chose not to analyse male and female cohorts separately, because we did not expect our sample size to be large enough to enable us to investigate all of the factors in which we were interested.

Advancing age was associated with higher age-standardised BMD. We consider this to be an artefact of the selection of patients via the pre-screening questionnaire. To be eligible for the study, younger people needed to have more severe disease than older patients. As discussed in the previous section, women had higher *Z*-scores than men. Therefore, female gender as associated with decreased incidence of low BMD at all three cutoffs listed ($Z<-1.0$, $Z<-1.5$, $Z<-2.0$). As expected, decreasing weight and low body mass index were significantly associated with low BMD.

Ever smoking was not associated with low BMD (the prevalence of ever-smoking was high in both groups), but increasing amount of pack years smoked was associated with low BMD in the $Z<-1.0$ and $Z<-1.5$ groups.

Use of medications for preventing or slowing bone loss, such as hormone replacement therapy, calcitriol, and calcium supplements were associated with low BMD in some *Z*-score groups. We observed that these medications were often prescribed to people who had a prior diagnosis of low BMD or were considered to be high risk of developing low BMD by their physicians, although we did not record whether or not people had a prior diagnosis of low bone density or not.

The number of booster courses of OCS was also related to low BMD - whether they had any or no courses of OCS with BMD $Z<-2.0$, the total number of courses with $Z<-1.0$ and the number of courses (split into categories) with $Z<2.0$. The direction of effect for two of the three variables with low BMD at $Z<-2.0$, is the opposite of what would be expected from previous research, with higher number of OCS courses associated with high BMD. The best explanation for this is that there were very few numbers of people with $Z<-2.0$, so a few spurious results related to the small sample

size are to be expected, and that the association of total number of courses with bone density $Z<-1.0$ is only just significant according to our criteria ($p<0.25$).

Table 39 – Univariate associations between low BMD and selected risk factors in men and women[§]

Risk factor	Z<-1.0	Z<-1.5	Z<-2.0	Direction of effect	Analysis method
Age	✓✓	×	×	(-)	Logistic regression
Menopause	×	×	×		χ^2 test
Age at menopause	×	×	×		χ^2 test
Gender	✓	✓	✓	(-) *	χ^2 test
Height	×	×	×		logistic regression
Weight	✓✓✓	✓✓	✓	(-)	logistic regression
BMI	✓✓✓	✓✓✓	✓	(-)	Logistic regression
Ever smoked	×	×	×		χ^2 test
Pack years	✓	✓✓✓	×	(+)	logistic regression
Current use:					
HRT	×	✓	✓✓	(-)	χ^2 test
Calcitriol	✓✓✓	✓✓✓	×	(+)	χ^2 test
Warfarin	×	✓✓	×	(+)	χ^2 test
Calcium use	✓	×	×	(+)	χ^2 test
Daily ICS	×	×	×		χ^2 test
Daily ICS dose (raw)	×	✓	×	(+)	logistic regression
Daily ICS dose (categories)	×	×	×		χ^2 test
Daily OCS	×	✓	✓		logistic regression
Theophylline		×	×		χ^2 test
Thyroxine	✓✓	×	×	(-)	χ^2 test
Anticonvulsants	×	×	×		χ^2 test
Ever use:					
Loop diuretics	×	×	×		χ^2 test
Thiazide diuretics	✓	✓	×	(-)	χ^2 test
Maternal fractures	✓	×	×	(+)	χ^2 test
Fractures since age 40	×	×	×		χ^2 test
Fractures at ribs or spine	✓✓	✓	×	(+)	χ^2 test
Rib fractures	✓✓	✓	×	(+)	χ^2 test
Spine fractures	×	✓	×	(+)	χ^2 test
Courses of OCS in last two years – any/none	×	×	✓✓	(-)	logistic regression
Number of OCS courses in last two years	✓	×	×	(+)	logistic regression
Number of OCS courses in last two years (categories)	×	×	✓	(-)	logistic regression
Respiratory admissions (number)	✓	×	✓	(+)	χ^2 test for ordered categories, logistic regression
Low exercise tolerance	×	✓	×	(-)	χ^2 test
Low leisure score	✓✓	✓	✓✓	(-)	χ^2 test
Low FEV_1 (divided into groups)	✓	✓✓✓	✓✓	(-)	χ^2 test

Legend:	× p>0.25	✓ p≤0.25	✓✓ p≤0.05	✓✓✓ p≤0.01

[§] Positive (+) effect direction indicates that the presence of the factor is associated with low BMD eg people who smoked cigarettes for a large number of pack years are more likely to have BMD Z<-1.5 than those who smoked for fewer pack years. Negative (-) effect direction indicates that the absence of the factor is associated with low BMD eg patients NOT taking thiazides are more likely to have BMD Z<-1.5 than those who have taken thiazides.

* Females had higher BMD

4.6 *Multivariate analysis for bone density cutoff of Z<-1.5*

Knowing that an individual risk factor is associated with low BMD has merit. However, some risk factors will be more strongly associated with low BMD than others, and some risk factors will measure similar things – and therefore will be co-linear. Therefore, identifying a group of risk factors that will predict low BMD when considered together will predict low BMD more accurately than individual risk factors, and will use the least number of risk factors by adjusting for strength of association and co-linearity. This requires multivariate analysis, and the process and results of the multiple logistic regression are discussed next.

4.6.1 Multivariate logistic regression

Variables that had an association with low BMD ($Z<-1.5$) of $p<0.25$ ("ticked" (✓) in Table 39) were included in the multivariate model. This approach was used because it reduced the number of factors entering the multivariate analysis, whilst still including factors with some association with low BMD into the analysis.

The variables that survived univariate analysis which were not included in the multivariate model were:

- "Current use of calcitriol"
- "ever use of thiazide diuretics"
- "weight"

This leaves the variables gender, BMI<20, >80 pack years smoked, maintenance OCS usage, ICS daily dosage, exercise tolerance, Baecke Leisure score, FEV_1 % predicted (separated into BTS groups), current use of hormone replacement therapy, current use of warfarin, fractures of the ribs or spine.

The reasons why these variables were not included are described as follows:

4.6.2 Current use of calcitriol

We chose not to include "Current use of calcitriol" in the multivariate analysis as it indicated that a patient was already being treated for low bone density. This argument is also appropriate for current use of hormone replacement therapy and calcium tablets, but not thiazide diuretics because thiazides are not used as a therapy for osteoporosis, nor was their effect on BMD widely recognised at the time this study was undertaken.

While we did not specifically ask whether or not individual patients had already been diagnosed as having low BMD, people are only able to obtain calcitriol via an authority prescription if the person has a demonstrated osteoporotic fracture.[203] While patients who have already had an osteoporotic fracture probably have low BMD, the purpose of our analysis was to develop a screening tool to find people at risk of having undiagnosed low bone density rather than finding patients already known to have low BMD.

4.6.3 Ever use of thiazide diuretics

Thiazides are medications prescribed primarily for hypertension. "Ever use" of thiazide diuretics was significantly associated with low BMD in the univariate analysis, but was omitted from the multivariate analysis due to "estimability". This is because patients who had "ever" taken thiazide diuretics or when ever-consumption of thiazides were "unknown" were all in the non-osteoporotic group at $Z<-1.5$ (See Table 40), and therefore Stata was unable to utilise this factor in the multivariate model. This was unfortunate, because thiazides are known to preserve low BMD in normotensive subjects randomised to thiazide treatment,[206] and to reduce hip fracture risk by around 30% in cohort studies of thiazide users.[233,234]

Table 40 – Ever use of thiazide diuretics for participants with low (Z<-1.5) and not-low (Z>-1.5) bone density

	Never	Ever	Unknown	Total
Z>-1.5	173 (77.93%)	11 (100%)	6 (100%)	190 (79.5%)
Z<-1.5	49 (22.07%)	0 (0%)	0 (0%)	49 (20.5%)
Total	222 (100%)	11 (100%)	6 (100%)	239 (100%)

4.6.4 Body size parameters

BMI was chosen in preference to weight as we considered that it provided more information on body build than weight alone.

However, there are additional considerations of interest surrounding the risk factor "weight" which will also be discussed.

4.6.5 Further considerations regarding "weight"

Adjustment for weight is made in the *Z*-score calculations for DXA to correct for technical errors in the calculation of the BMD values related to soft tissue effects in the reference population (higher weight is associated with higher BMD and vice versa). These equations are as follows and are applied for weights 25-100 kg.

N.B. No-one in our sample had weight below 25kg, and 13 patients had weight above 100kg (13/39=5.4%), with the heaviest weight of any subject being 135kg.

Table 41 – Weight regression for reference females[10]

Site	Regression equation	r
Anterior-posterior spine	BMD=0.845 + (0.004 x Weight)	0.14
Neck of femur	BMD=0.670 + (0.003x Weight)	0.28

Evidently the adjustment made to *Z*-scores to standardise weight is only slight. However, weight must have an effect over and above technical considerations because weight survived to the multivariate analysis in our study population.

One possible reason for this is that the population studied by us is sufficiently dissimilar to the reference population.

The reference population were white ambulatory subjects from the general population who were free from chronic diseases affecting bone (like asthma), and were not taking medications known to influence bone density (eg corticosteroids, thyroxine, estrogen). This would have excluded the vast majority of participants in our study sample. Therefore, our sample is likely to differ in a number of ways.

Examples include:

- 80% of sample were currently taking corticosteroids
- 8.8% of sample were currently taking thyroxine

- Mean BMI significantly different from "normal" BMI as per original research[116] (See Table 42)
- Mean leisure scores were significantly different from the original cohort[209] (See Table 43), although the original cohort were young Dutch men and women aged 19-31, not older Australians (mean age of our sample 65±8 years).

The weight and activity levels of people in the general population of all ages may have changed since the early 1980's when the research by Garrow *et al* and Baecke *et al* were published.[116,209] This has not been taken into account when comparing our population to the reference population.

Table 42 – Mean BMI for our sample compared to "normal" BMI

	"Normal" BMI (reference population[116])	BMI Mean±SD (our sample)	p-value (one sample t-test)
Women	22.5	28.0±6.4	<0.001
Men	22.5	25.7±4.3	<0.001

Table 43 – Baecke leisure scores for original cohort and our sample

	Original cohort[209]	Our sample	p-value (one sample t-test)
Men	2.8±0.1	1.0±0.7	<0.001
Women	3.1±0.0	0.9±0.1	<0.001

Other factors may also explain this phenomena. Weight and physical build may have an effect on bone density in addition to the technical readings by the DXA machine, and these must be independent of age (as comparisons are standardised for age in *Z*-score calculations). Such factors could include increased skeletal loading (and hence increased BMD) with increased weight. Further considerations about weight and true BMD as measured by DXA are discussed in Chapter 3.9 on page 59.

4.6.6 Dichotomising continuous variables

Receiver operating characteristic (ROC) curves were constructed for continuous variables that had survived the univariate analysis (BMI, pack years, FEV_1 % predicted) to determine cut-off points at which the continuous variable could be dichotomised. The cutoff points chosen were BMI=20 and pack years=80. There was no useful cutoff point for FEV_1, which would have enabled the variable to be dichotomised, therefore the variable was left grouped into the four categories used in the British Thoracic Guidelines[212] (FEV_1<80; 60-80; 40-60; <40% predicted).

The leisure score variable was set to choose the most important category of this variable should it exist by using the "indicator" function of Stata. P-value for entry was set at p=0.1 for the multiple stepwise logistic regression.

Four factors remained after multiple logistic regression had been applied to the data.

These were:

- BMI<20 (kg/m^2)
- Pack years>80
- Current use of warfarin
- FEV_1 group (grouped according to British Thoracic Society criteria[212])

These four factors, when considered together, were a good fit to the model (assessed using Mantel Haensel χ^2 test for goodness of fit). These factors and associated odds ratios are listed in Table 44.

Factors surviving multiple logistic regression

Table 44 - Factors surviving multiple logistic regression

	Odds ratio	Standard error	p-value	95% confidence interval (CI)	
BMI <20	3.49	1.71	0.01	1.34	9.10
Pack years >80	2.46	1.14	0.051	1.00	6.08
Current use warfarin	5.10	3.55	0.019	1.31	19.92
FEV_1 % predicted, grouped §	1.35	0.23	0.072	0.97	1.88

Goodness of fit $\chi^2(14)=11.35$, p=0.65 (reject good fit if p≤0.05)
Area under the ROC curve 0.7
§ Grouped according to British Thoracic Guidelines[212]

Therefore, having a BMI <20 increased the odds of having BMD *Z*<-1.5 by ~3.5x , smoking more than 80 pack years increased the odds by ~2.5x, and currently using warfarin increased the odds by 5.1x. Having FEV_1 60-80% of predicted increased the odds of having BMD *Z*<-1.5 by 1.35x; having FEV_1 40-60% predicted by 1.82x ($=1.35^2$); and having FEV_1 less than 40% predicted by 2.46x ($=1.35^3$).

4.7 Sensitivity and specificity

We calculated the sensitivity and specificity of the use of four risk factors to predict patients who had BMD of Z<-1.5. The sensitivity-specificity curves are illustrated in Figure 16 and the area under the ROC curve is 0.7 (see Figure 17).

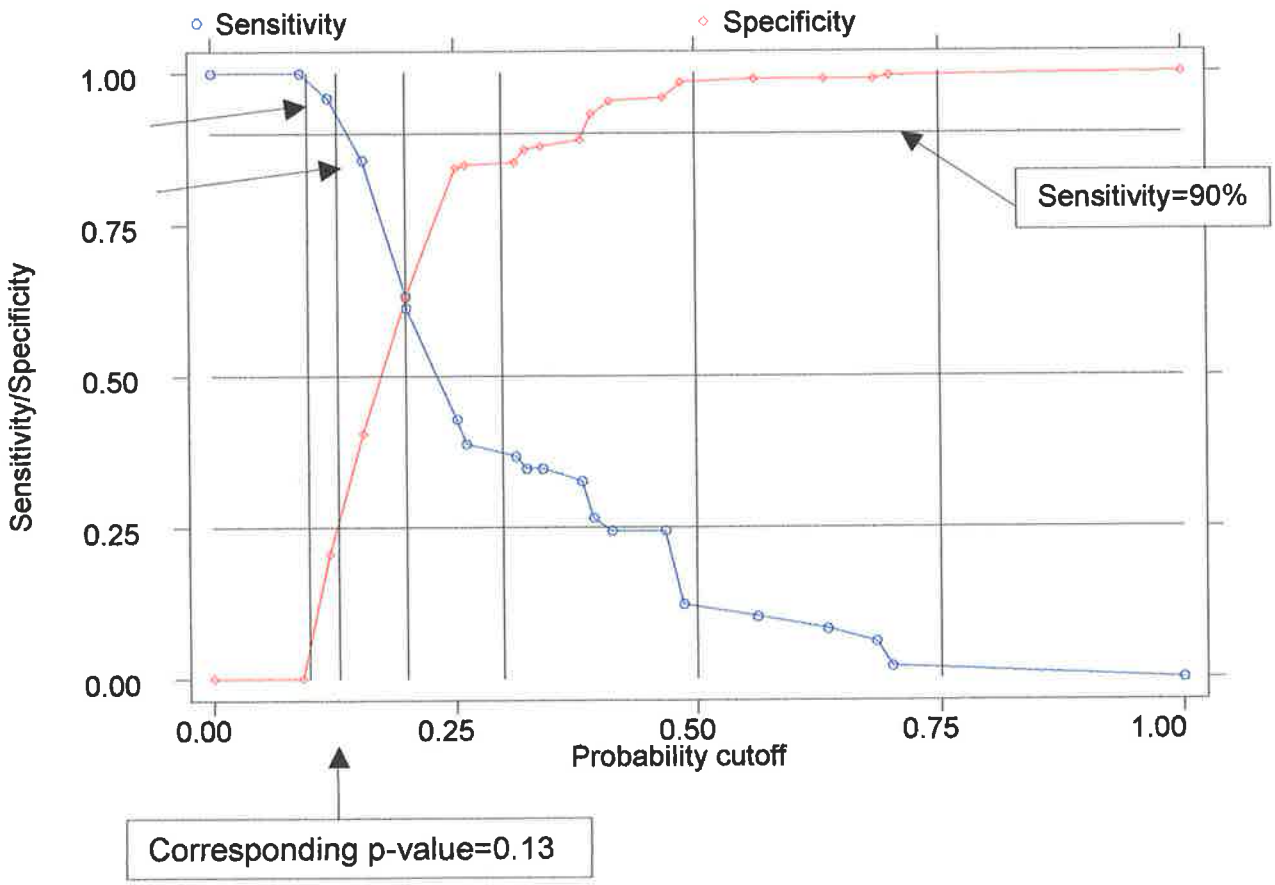


Figure 16 - Sensitivity and specificity of risk factor model

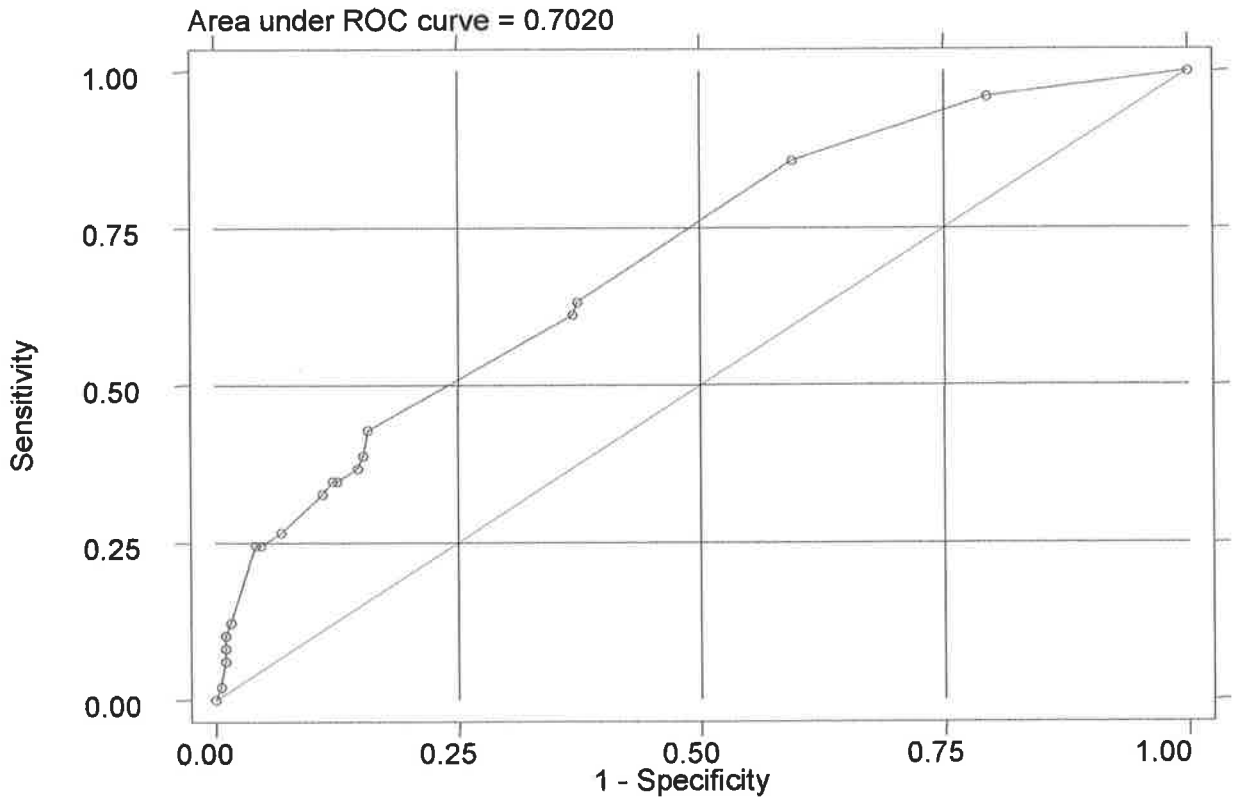


Figure 17 - Receiver operating characteristic (ROC) curve for factors surviving multivariate model with probability cutoff p=0.13 (Table 44)

There was no probability cutoff that corresponded to the target of 90% sensitivity in our data (see two dots indicated by arrows in Figure , either side of the line indicating 90% sensitivity). Therefore, the closest approximations to 90% sensitivity in our data was p=0.13 with a corresponding sensitivity of 85.71% (See Table 45).

This mix of sensitivity and specificity corresponds to a probability level of 0.13 and sensitivity of 86% (See Table 46) is preferable to the mix which corresponds to a higher probability level of 0.12 with sensitivity of 96% (See Table 46). With the higher sensitivity level, patients identified by the test as having low BMD are more likely to actually have low BMD. However, the specificity is poorer (21% compared to 41%), and only 36% (compared to 50%) of patients are correctly classified as either having low BMD, or not having low BMD. These high values of sensitivity also result in high rates of false positive results – 60% with p=0.13, and 80% with p=0.12.

Table 45 - Logistic model for *Z*<-1.5 at cutoff level p=0.13, yielding sensitivity of 86% and specificity of 45%

Classified	True D	True ~D	Total
+	42	113	155
-	7	77	84
Total	49	190	239

Classified + if predicted Pr(D) >= .13
True D defined as z_15n ~= 0

Sensitivity	Pr(+| D)	85.71%
Specificity	Pr(-|~D)	40.53%
Positive predictive value	Pr(D| +)	27.10%
Negative predictive value	Pr(~D| -)	91.67%
False + rate for true ~D	Pr(+|~D)	59.47%
False - rate for true D	Pr(-| D)	14.29%
False + rate for classified +	Pr(~D| +)	72.90%
False - rate for classified -	Pr(D| -)	8.33%
Correctly classified		49.79%

Table 46 - Logistic model for *Z*<-1.5 at cutoff level p=0.12, yielding sensitivity of 96% and specificity of 21%

Classified	True D	True ~D	Total
+	47	151	198
-	2	39	41
Total	49	190	239

Classified + if predicted Pr(D) >= .12
True D defined as z_15n ~= 0

Sensitivity	Pr(+| D)	95.92%
Specificity	Pr(-|~D)	20.53%
Positive predictive value	Pr(D| +)	23.74%
Negative predictive value	Pr(~D| -)	95.12%
False + rate for true ~D	Pr(+|~D)	79.47%
False - rate for true D	Pr(-| D)	4.08%
False + rate for classified +	Pr(~D| +)	76.26%
False - rate for classified -	Pr(D| -)	4.88%
Correctly classified		35.98%

4.8 Summary of selected model

The logistic model finally selected as a fit to this data has characteristics as seen in Table 45 – sensitivity of 86%, specificity of 41%, positive predictive value =27%, negative predictive value =92%, with 50% of patients correctly classified ((42+77)/239=50%).

This model was chosen in preference to a logistic model fitting this data that had sensitivity over 90%. This model had sensitivity of 96%, specificity of 21%, positive predictive value of 24%, negative predictive value of 95%, and correctly classified only 36% of patients. Patients that the model labelled as having Z>-1.5 had a 12% chance of having low BMD. Whilst this model missed less people who had BMD Z-score of Z<-1.5 at the lumbar spine, neck of femur or total femur, it misclassified many more as having low BMD who in reality had normal BMD.

Participants who had a likelihood of having low BMD of more than the cutoff value of p=0.13, corresponding to the sensitivity and specificity parameters shown in Figure 17 could be recommended to have a screening DXA. This applies to participants who had any of:

- BMI<20
- Smoked for >80 pack years
- Currently using warfarin
- FEV_1 ≤60% predicted

This corresponds to 65% of our sample (155/239).

However, a more useful approach is to recommend that patients who *do not* have the criteria above *are not* recommended for screening DXA. There are two combinations of risk factors to which this probability applies (See Table 47).

The best use of this screening tool would be as a pre-DXA tool to identifying those who do NOT require screening with DXA. This would apply to the subjects who do NOT have any of the risk factors listed above and who therefore have less than 13% chance of having low BMD, of which there are two combinations of risk factors (See Table 47).

Table 47 – Combinations of risk factors with $p \leq 0.13$

Scenario	Probability of $Z<-1.5$	BMI<20	Pack years >80	Current warfarin use	FEV_1 (% predicted)	% of participants
1	9%	×	×	×	>80%	17%
2	12%	×	×	×	60-80%	18%

Therefore, the use of our pre-screening tool would reduce the use of DXA by around 35%.

Therefore, of the patients recommended for DXA, 27% would have low BMD ($Z<-1.5$) (positive predictive value), and of the patients NOT recommended for DXA, 92% would NOT have $Z<-1.5$ (negative predictive value). Eight percent of patients were not recommended for DXA but did have BMD $Z<-1.5$ (false negatives) - these patients would miss being identified as having low BMD in the first instance, although they may be able to be identified and re-screened at later visits to their general practitioner or respiratory physician.

4.8.1 Comment on confidence intervals in Table 44

Of the four factors which survived multiple logistic regression (listed in Table 44), the risk factor "Pack years >80" has a 95% confidence interval which touches 1 (1.00 → 6.08), and "FEV_1 % predicted, grouped" crosses over 1 (0.97 → 1.88). Therefore it is possible that these two factors have odds ratios that are not statistically significant as the "true" odds ratio may be 1 or close to 1 (where 1 is "no effect" or the same as "controls").

To be more sure that all the risk factors used to predict whether or not patients will have low BMD are statistically significant, the p-value for entry to the multiple logistic regression could be reduced from p=0.1 to p=0.05. This results in the reduction of the number of risk factors from 4 to 3 (FEV_1 % predicted, grouped drops out), and the 95% confidence intervals do not cross 1, and the odds ratios and standard errors adjust slightly (See Table 48).

Table 48 – Factors surviving multiple logistic regression when p-value for entry to the logistic model is p=0.05

	Odds ratio	Standard error	p-value	95% confidence interval (CI)	
BMI <20	4.24	0.02	0.002	1.67	10.76
Pack years >80	2.89	1.30	0.019	1.20	7.00
Current use warfarin	4.30	2.92	0.032	1.14	16.31

Goodness of fit $\chi^2(2)=0.01$, p=0.9971 (reject good fit if p≤0.05)
Area under the ROC curve 0.65

However, the logistic models resulting from the analysis in Table 48 which are close to 90% sensitivity are:

Analysis from Table 48 - Model 1: Sensitivity=45%, specificity=84%, positive predictive value=41%, negative predictive value =85%, correctly classifying 75% of patients.

Analysis from Table 48 - Model 2: Sensitivity=100%, specificity=0%, positive predictive value=21%, negative predictive value null, correctly classifying 21% of patients.

Either Model 1 or Model 2 above would be poor screening tests. Model 1 would miss half the patients who had low BMD (false negative rate of 55%), and Model 2 would result in *all* patients being recommended for DXA.

Therefore, I consider that the logistic model described in Table 44 and Table 45 with sensitivity of 86% and specificity of 41% is better than either Model 1 or Model 2 resulting from the analysis in Table 48.

I also consider that the risk that some of the risk factors described in Table 44 may not be statistically significant is less than the inefficiencies that would result from using either Model 1 or Model 2 resulting from the analysis in Table 48 as a tool for selecting who should receive a DXA.

4.9 Further analysis by site and gender

Despite reservations about the limited power to detect differences with these sample sizes, analyses for associations between study factors and individual anatomical sites (spine and femur separately) by gender have been presented over the following pages in Table 49 to Table 54 on pages 125-130, except treatments for low BMD (HRT, calcitriol and calcium tablets but not thiazides) using the rationale already described in 4.6.2 Current use of calcitriol on page 113. As per the previous analyses, risk factors that were associated with low BMD ($p<0.25$) at the particular site and gender in question were used in the multivariate logistic regressions (See Table 55 to Table 58 on pages 131 to 134). Stepwise (multiple) logistic regression with a p-value for entry to the model of $p=0.1$ was used. Surviving continuos variables were dichotomised using the same cut-off points as in the earlier analyses (See 4.6.6 Dichotomising continuous variables on page 116), as long as dichotomising the variable did not alter the model such that the pseudo R^2 was greatly reduced, or the goodness of fit was poor. In these cases, the continuous variable was retained. Any risk factors that the model could not use for reasons such as "estimability" were excluded from the multivariate analysis for the reasons previously described (See 4.6.3 Ever use of thiazide diuretics on page 114).

Table 49 – Univariate associations between low spine BMD and selected risk factors in men and women[§]

Risk factor	Z<-1.0	Z<-1.5	Z<-2.0	Direction of effect	Analysis method
N=	54	29	11		
Age	✓✓✓	✓	×	(-)	Logistic regression
Menopause	✓	×	×	(-)	χ^2 test
Age at menopause	×	×	×		χ^2 test
Gender	×	×	×		χ^2 test
Height	×	×	×		logistic regression
Weight	✓✓	✓	×	(-)	logistic regression
BMI	✓✓	✓	✓	(-)	Logistic regression
Ever smoked	×	×	×		χ^2 test
Pack years	×	×	×		logistic regression
Current use:	×	×	✓	(-)	
HRT	×	×	×		χ^2 test
Calcitriol	×	×	×		χ^2 test
Warfarin	✓	✓	×	(+)	χ^2 test
Calcium use	×	×	×		χ^2 test
Daily ICS	×	×	✓	(+)	χ^2 test
Daily ICS dose (raw)	×	×	✓	(+)	logistic regression
Daily ICS dose (categories)	×	×	×		χ^2 test
Daily OCS	×	×	✓	(+)	logistic regression
Theophylline	×	×	×		χ^2 test
Thyroxine	×	×	×		χ^2 test
Anticonvulsants	✓	×	×	(+)	χ^2 test
Ever use:	×	×	×		
Loop diuretics	✓	×	×	(-)	χ^2 test
Thiazide diuretics	×	×	×		χ^2 test
Maternal fractures	✓	×	×	(+)	χ^2 test
Fractures since age 40	×	×	×		χ^2 test
Fractures at ribs or spine	×	×	×		χ^2 test
Rib fractures	×	×	✓	(+)	χ^2 test
Spine fractures	×	×	×		χ^2 test
Courses of OCS in last two years – any/none	×	✓	✓	(-)	logistic regression
Number of OCS courses in last two years	×	×	×		logistic regression
Number of OCS courses in last two years (categories)	×	×	×		logistic regression
Respiratory admissions (number)	×	×	×		χ^2 test for ordered categories, logistic regression
Low exercise tolerance	×	×	×		χ^2 test
Leisure score	×	✓✓	✓	(-)	χ^2 test
FEV_1 (divided into groups)	×	×	✓	(-)	χ^2 test

Legend:	× p>0.25	✓ p≤0.25	✓✓ p≤0.05	✓✓✓ p≤0.01

[§] Positive (+) effect direction indicates that the presence of the factor is associated with low BMD eg people who smoked cigarettes for a large number of pack years are more likely to have BMD Z<-1.5 than those who smoked for fewer pack years. Negative (-) effect direction indicates that the absence of the factor is associated with low BMD eg patients NOT taking thiazides are more likely to have BMD Z<-1.5 than those who have taken thiazides.

Table 50 - Univariate associations between low spine BMD and selected risk factors in women

Risk factor	Z<-1.0	Z<-1.5	Z<-2.0	Direction of effect	Analysis method
N=	31	15	5		
Age	✓	✓	×	(-)	Logistic regression
Menopause	✓	✓	×	(-)	χ^2 test
Age at menopause	×	×	×		χ^2 test
Height	✓	✓	×	(-)	logistic regression
Weight	✓	✓✓✓	✓	(-)	logistic regression
BMI	✓✓✓	✓✓✓	×	(-)	Logistic regression
Ever smoked	×	×	✓	(+)	χ^2 test
Pack years	✓	✓	×	(-)	logistic regression
Current use:					
HRT	×	×	×		χ^2 test
Calcitriol	✓	✓	×	(+)	χ^2 test
Warfarin	×	×	×		χ^2 test
Calcium use	✓	✓	✓	(+)	χ^2 test
Daily ICS	×	×	×		χ^2 test
Daily ICS dose (raw)	×	×	×		logistic regression
Daily ICS dose (categories)	×	×	×		χ^2 test
Daily OCS	×	×	×		logistic regression
Theophylline	✓	✓	×	(-)	χ^2 test
Thyroxine	×	×	×		χ^2 test
Anticonvulsants	×	×	×		χ^2 test
Ever use:					
Loop diuretics	✓✓	✓✓	×	(-)	χ^2 test
Thiazide diuretics	×	×	×		χ^2 test
Maternal fractures	✓	✓	×	(+)	χ^2 test
Fractures since age 40	×	×	×		χ^2 test
Fractures at ribs or spine	×	×	×		χ^2 test
Rib fractures	×	×	×		χ^2 test
Spine fractures	×	×	×		χ^2 test
Courses of OCS in last two years – any/none	×	×	✓	(-)	logistic regression
Number of OCS courses in last two years	×	×	✓	(-)	logistic regression
Number of OCS courses in last two years (categories)	×	×	×		logistic regression
Respiratory admissions (number)	×	×	×		χ^2 test for ordered categories, logistic regression
Low exercise tolerance	×	×	✓	(-)	χ^2 test
Leisure score	×	×	×		χ^2 test
Low FEV_1 (divided into groups)	×	×	✓	(-)	χ^2 test

Legend:	× p>0.25	✓ p≤0.25	✓✓ p≤0.05	✓✓✓ p≤0.01

Table 51 – Univariate associations between low spine BMD and selected risk factors in men

Risk factor	Z<-1.0	Z<-1.5	Z<-2.0	Direction of effect	Analysis method
N=	23	14	6		
Age	✓	✓✓	✓	(-)	Logistic regression
Height	×	×	×		logistic regression
Weight	×	×	×		logistic regression
BMI	×	×	×		Logistic regression
Ever smoked	×	✓	✓✓	(-)	χ^2 test
Pack years	×	×	×		logistic regression
Current use:					
HRT	×	×	×		χ^2 test
Calcitriol	×	×	×		χ^2 test
Warfarin	✓✓	✓	✓	(+)	χ^2 test
Calcium use	×	✓	✓	(-)	χ^2 test
Daily ICS	✓	✓	✓	(+)	χ^2 test
Daily ICS dose (raw)	✓	✓	✓	(+)	logistic regression
Daily ICS dose (categories)	✓	✓	×	(+)	χ^2 test
Daily OCS	×	×	✓	(+)	logistic regression
Theophylline	×	×	×		χ^2 test
Thyroxine	×	✓	✓✓	(+)	χ^2 test
Anticonvulsants	✓	×	×	(+)	χ^2 test
Ever use:					
Loop diuretics	×	×	×		χ^2 test
Thiazide diuretics	×	×	×		χ^2 test
Maternal fractures	×	×	×		χ^2 test
Fractures since age 40	×	×	×		χ^2 test
Fractures at ribs or spine	×	✓	✓	(+)	χ^2 test
Rib fractures	×	✓	✓	(+)	χ^2 test
Spine fractures	×	✓	×	(+)	χ^2 test
Courses of OCS in last two years – any/none	×	✓	×	(-)	logistic regression
Number of OCS courses in last two years	×	×	×		logistic regression
Number of OCS courses in last two years (categories)	×	×	×		logistic regression
Respiratory admissions (number)	×	×	×		χ^2 test for ordered categories, logistic regression
Low exercise tolerance	×	×	×		χ^2 test
Leisure score	×	✓	✓	(-)	χ^2 test
FEV_1 (divided into groups)	✓	×	✓	(-)	χ^2 test

Legend:	× p>0.25	✓ p≤0.25	✓✓ p≤0.05	✓✓✓ p≤0.01

Table 52 – Univariate associations between low femur BMD and selected risk factors in men and women

Risk factor	Z<-1.0	Z<-1.5	Z<-2.0	Direction of effect	Analysis method
N=	70	31	10		
Age	×	×	×		Logistic regression
Menopause	×	×	×		χ^2 test
Age at menopause	×	×	×	Males have	χ^2 test
Gender	✓✓	✓✓	✓✓	lower BMD	χ^2 test
Height	×	×	✓	(-)	logistic regression
Weight	✓✓✓	✓✓✓	✓	(-)	logistic regression
BMI	✓✓✓	✓✓✓	✓	(-)	Logistic regression
Ever smoked	×	✓	×	(+)	χ^2 test
Pack years	✓✓	✓✓✓	✓	(+)	logistic regression
Current use:					
HRT	×	✓	✓	(-)	χ^2 test
Calcitriol	✓✓✓	✓✓✓	×	(+)	χ^2 test
Warfarin	×	×	×		χ^2 test
Calcium use	×	×	✓	(-)	χ^2 test
Daily ICS	×	×	×		χ^2 test
Daily ICS dose (raw)	×	×	✓	(-)	logistic regression
Daily ICS dose (categories)	✓	×	×	(-)	χ^2 test
Daily OCS	×	✓	×	+	logistic regression
Theophylline	×	×	×		χ^2 test
Thyroxine	✓	✓	×	(-)	χ^2 test
Anticonvulsants	×	×	×		χ^2 test
Ever use:					
Loop diuretics	×	✓(+)	✓(-)		χ^2 test
Thiazide diuretics	✓	×	×	(-)	χ^2 test
Maternal fractures	×	×	×		χ^2 test
Fractures since age 40	✓	✓✓	×	(+)	χ^2 test
Fractures at ribs or spine	✓✓✓	✓✓✓	×	(+)	χ^2 test
Rib fractures	✓✓✓	✓✓✓	✓	(+)	χ^2 test
Spine fractures	×	✓	×	(+)	χ^2 test
Courses of OCS in last two years – any/none	×	×	✓	(-)	logistic regression
Number of OCS courses in last two years	✓	✓	×	(+)	logistic regression
Number of OCS courses in last two years (categories)	×	×	×		logistic regression
Respiratory admissions (number)	✓✓	✓	×	(+)	χ^2 test for ordered categories, logistic regression
Low exercise tolerance	✓	✓✓	×	(-)	χ^2 test
Leisure score	✓✓✓	✓	✓✓	(-)	χ^2 test
FEV_1 (divided into groups)	✓✓	✓✓✓	✓	(-)	χ^2 test

Legend:	× p>0.25	✓ p≤0.25	✓✓ p≤0.05	✓✓✓ p≤0.01

Table 53 – Univariate associations between low femur BMD and selected risk factors in women

Risk factor	Z<-1.0	Z<-1.5	Z<-2.0	Direction of effect	Analysis method
N=	34	13	2		
Age	×	✓✓	×	(+)	Logistic regression
Menopause	×	×	×		χ^2 test
Age at menopause	×	×	✓	(-)	χ^2 test
Height	✓	✓	×	(-)	logistic regression
Weight	✓✓✓	✓✓✓	✓	(-)	logistic regression
BMI	✓✓✓	✓✓✓	✓✓✓⌘	(-)	Logistic regression
Ever smoked	×	✓	×		χ^2 test
Pack years	×	✓	×		logistic regression
Current use:					
HRT	×	✓	×	(-)	χ^2 test
Calcitriol	✓✓	✓✓	×	(+)	χ^2 test
Warfarin	×	×	×		χ^2 test
Calcium use	×	✓	×	(+)	χ^2 test
Daily ICS	×	×	✓	(-)	χ^2 test
Daily ICS dose (raw)	✓	✓	×	(+)	logistic regression
Daily ICS dose (categories)	✓	×	×	(+)	χ^2 test
Daily OCS	×	×	×		logistic regression
Theophylline	×	✓	×	(-)	χ^2 test
Thyroxine	✓✓	✓	×	(-)	χ^2 test
Anticonvulsants	×	×	×		χ^2 test
Ever use:					
Loop diuretics	×	✓✓	×	(+)	χ^2 test
Thiazide diuretics	×	×	×		χ^2 test
Maternal fractures	×	×	×		χ^2 test
Fractures since age 40	×	×	×		χ^2 test
Fractures at ribs or spine	×	×	×		χ^2 test
Rib fractures	×	✓	×	(+)	χ^2 test
Spine fractures	×	×	×		χ^2 test
Courses of OCS in last two years – any/none	×	×	✓✓✓‡	(-)	logistic regression
Number of OCS courses in last two years	×	×	✓✓✓‡	(-)	logistic regression
Number of OCS courses in last two years (categories)	×	×	✓	(-)	logistic regression
Respiratory admissions (number)	✓✓✓	✓✓	×	(+)	χ^2 test for ordered categories, logistic regression
Low exercise tolerance	✓✓	✓✓✓	✓	(-)	χ^2 test
Leisure score	✓✓	✓✓	✓	(-)	χ^2 test
FEV_1 (divided into groups)	✓✓	✓✓	✓✓✓¥	(-)	χ^2 test

⌘ BMI<=17.2248 fits data perfectly
‡ Using no courses of OCS in last 2 years predicts Z<-2.0 perfectly
¥ FEV_1 <40% predicted predicts Z<-2.0 perfectly

Legend:	× p>0.25	✓ p≤0.25	✓✓ p≤0.05	✓✓✓ p≤0.01

Table 54 – Univariate associations between low femur BMD and selected risk factors in men

Risk factor	Z<-1.0	Z<-1.5	Z<-2.0	Direction of effect	Analysis method
N=	36	18	8		
Age	✓	✓	×	(-)	Logistic regression
Height	✓	×	×	(-)	logistic regression
Weight	✓✓	✓	×	(-)	logistic regression
BMI	✓✓(-)	✓	×(+)		Logistic regression
Ever smoked	✓✓	✓	✓		χ^2 test
Pack years	✓	✓	×	(+)	logistic regression
Current use:					
HRT	✓	×	×		χ^2 test
Calcitriol	×	✓	×	(+)	χ^2 test
Warfarin	×	×	×		χ^2 test
Calcium use	×	×	×		χ^2 test
Daily ICS	×	×	×		χ^2 test
Daily ICS dose (raw)	×	×	✓	(-)	logistic regression
Daily ICS dose (categories)	×	×	×		χ^2 test
Daily OCS	×	✓	×	(+)	logistic regression
Theophylline	×	✓	✓	(-)	χ^2 test
Thyroxine	×	×	×		χ^2 test
Anticonvulsants	×	×	×		χ^2 test
Ever use:					
Loop diuretics	×	×	✓	(-)	χ^2 test
Thiazide diuretics	×	×	×		χ^2 test
Maternal fractures	×	×	×		χ^2 test
Fractures since age 40	✓✓	✓	×	(+)	χ^2 test
Fractures at ribs or spine	✓✓	✓✓✓	✓	(+)	χ^2 test
Rib fractures	✓✓✓	✓✓	✓	(+)	χ^2 test
Spine fractures	✓	✓✓		(+)	χ^2 test
Courses of OCS in last two years – any/none	×	✓	×	(+)	logistic regression
Number of OCS courses in last two years	✓	✓✓	×	(+)	logistic regression
Number of OCS courses in last two years (categories)	✓	✓	×	(+)	logistic regression
Respiratory admissions (number)	✓✓	×	×		χ^2 test for ordered categories, logistic regression
Low exercise tolerance	×	×	✓	(-)	χ^2 test
Leisure score	✓	✓	✓	(-)	χ^2 test
FEV_1 (divided into groups)	✓	×	×	(-)	χ^2 test

Legend:	× p>0.25	✓ p≤0.25	✓✓ p≤0.05	✓✓✓ p≤0.01

Table 55 – Multivariate analysis of associations between low spine BMD and selected risk factors

		Men and women										
	N =	Variables included [OR (SE)]	Prob-ability of "low BMD"	Sens-itivity	Spec-ificity	PPV	NPV	Correctly classifies (%)	Model goodness of fit	Variation Explained (Pseudo R2)	AU ROC	Applies to % of population	Don't need DXA
Z<-1.0	54	BMI<20 [6.7 (3.2)] age (groups) [1/1.3 (1/14)] warfarin [4 (2.8)]	0.15	83	37	28	88	47	0.61	9%	0.7	32%	*age 65+ & BMI>20 & not using warfarin
Z<-1.5	29	BMI<20 [5.4 (2.9)] warfarin [5.4 (4.0)] age [1/10 (1/40)] used OCS in >2yrs [1/2.2 (1/5.1)]	0.065	90	31	15	96	38	0.53	9%	0.71	29%	*age >65 & BMI>20, not using warfarin & have taken OCS in last 2 years
Z<-2.0	11	FEV1 grouped [2.8 (1.2)] any/no OCS in <2 yrs [1/4 (1/6)] daily OCS	0.022	91	49	8	99	51	0.74	16%	0.80	47%	*FEV1>60% predicted
		WOMEN											
Z<-1.0	31	BMI<20 [30 (24)] age (groups) [0.7 (0.09)] theophylline [1/7 (1/6)]	0.095	90	26	26	90	40	0.89	20%	0.76	22%	*BMI>20 & aged >75 yrs *BMI>20 taking theophylline
Z<-1.5	15	BMI [0.92 (1/2)]	0.07	93	21	13	96	30	0.60	4%	0.61	18%	BMI>33
Z<-2.0	5	FEV1 grouped [3.9 (2.4)] OCS dose in <2 years (grouped) [1/5.5 (1/6.3)]	0.05	80	84	16	99	84	0.92	24%	0.9	82%	*FEV1>40 predicted & >1 courses OCS in 2 yrs
		MEN											
Z<-1.0	23	Age (grouped) [1/8 (1/3)] Current use of warfarin [6 (5.7)]	0.15	78	47	31	88	54	0.53	7%	0.67	41%	*Aged over 70 years and not taking warfarin
Z<-1.5	14	Age (grouped) [2/3 (1/8) Current use of thyroxine [19.6 (30)] Spine fractures [12 (18)]	0.08	86	44	20	95	50	0.47	11%	0.73	40%	*Aged over 70 years and not taking thyroxine, no spine #
Z<-2.0	6	Thyroxine [28 (43)] Rib fractures [7 (7)]	no model better than chance										

Table 56 - Multivariate analysis of associations between low femur BMD and selected risk factors in men and women

	N =	Model includes	Prob-ability of "low BMD"	Sens-itivity	Spec-ificity	PPV	NPV	% Correctly classified	Model goodness of fit	Variation Explained (Pseudo R2)	AU ROC	Applies to % of population	Don't need DXA
Z<-1.0	70	BMI>20 [10 (5.6)] Baecke leisure score (grouped) [1/2 (1/8)] rib fracture since age 40 [3.6 (2.0)] gender [1/2 (1/5)] (female=1, male=0) respiratory admissions in 5yrs [1.3 (1.5)]	0.15	91	31	35	90	49	0.0043	17	0.76	24%	BMI>20 & no rib # & medium or high leisure index
Z<-1.5	31	BMI>20 [4 (2.3)] FEV1 grouped [2 (1/2)] rib fracture since age 40 [3.4 (1.9)] Pack years>80 [3.4 (1.9)] Current use of theophylline [1/8 (1/7)]	0.08	90	51	21	97	56	0.1018	21%	0.79	45%	*>60% predicted & BMI>20 & no rib # & *FEV1<60% predicted & taking theophylline
Z<-2.0	10	BMI>20 [5.5 (4.2)] Smoked >80 pack years [4.2 (3.2)] Daily dose ICS (ug) [0.99 (0.0006)]	0.02	80	53	7	98	54	0.1025	11%	0.74	51%	*ICS daily dose >1000ug & BMI>20 &<80 pack years

Table 57 - Multivariate analysis of associations between low femur BMD and selected risk factors in women

	N =	Model includes	Probability of "low BMD"	Sens-itivity	Spec-ificity	PPV	NPV	Correctly classifies (%)	Model goodness of fit	Variation Explained (Pseudo R2)	AU ROC	Applies to % of population	Don't need DXA
Z<-1.0	34	BMI>20 [50.7 (48)] Baecke leisure score (grouped) [1/3 (1/8)] respiratory admissions in 5yrs [1.8 (0.5)] ICS dose (grouped) [1.9 (2/3)]	0.095	91	49	36	94	60	0.053	30%	0.83	39%	*Leisure score medium & BMI>20 *Leisure score low & BMI>20 & ICS <1000 μg/day *Leisure score very low & BMI>20 & no respiratory admissions & not using ICS
Z<-1.5	13	BMI>20 [10.8 (9.8)] FEV1 (grouped) [4.2 (2.1)] Baecke leisure score (grouped) [1/3 (1/5)] Age (grouped) [1.6 (1/2.3)]	0.1	92	83	36	99	84	1.000	42%	0.94	43%	*BMI>20 & Baecke leisure score medium or high & FEV1>40 % predicted *BMI>20 & low Baecke leisure score & FEV1>60% *BMI>20 & very low Baecke leisure score & FEV1>80%
Z<-2.0	2	BMI<=17.2248, FEV1<40% predicted, 0 courses OCS in last 2 years all predict BMD of Z<-2.0 perfectly											

Table 58 - Multivariate analysis of associations between low femur BMD and selected risk factors in men

	N =	Model includes	Probability of "low BMD"	Sens-itivity	Spec-ificity	PPV	NPV	Correctly classifies (%)	Model goodness of fit	Variation Explained (Pseudo R2)	AU ROC	Applies to % of population	Don't need DXA
Z<-1.0	36	Ribs [17.2 (18.6)] Weight [0.97 (1/6)]	0.24	92	34	44	88	55	0.3	14%	0.72	25%	*No rib fractures, weight >85 kg
Z<-1.5	18	Ribs [18 (17) Pack years [(1.02 (1/100)] Daily OCS [9.3 (7.7)] Baecke leisure score (grouped) [3 (1.7)] Theophylline [1/13 (1/10)]	0.1	89	60	33	96	65	0.74	28%	0.86	57%	*Leisure score medium & not taking daily OCS, no rib # & not taking theophylline *Leisure score medium & 25 pack years smoked, not taking daily OCS *Low leisure score, <110 PY, & not taking theophylline *Very low leisure score, no rib # & not taking daily OCS *Very low leisure score & taking theophylline
Z<-2.0	8	none											

Analysing the data in this manner shows the difference in selection factors between males and females and between spine and femur. The following risk factors survive multivariate analyses (as listed in Table 55 to Table 58 on pages 131-134.)

Table 59 – Risk factors surviving multivariate analysis: data subgrouped by age and gender[§]

	Women	Men	Both genders
Spine	• BMI>20 • younger age group • current non-use of theophylline • OCS use in the last 2 years	• current use of warfarin • current use of thyroxine • spine fractures • rib fractures	• younger age group
Femur	• BMI>20 • younger age group • low Baecke leisure scores • higher number of respiratory admissions in the last 5 years • OCS dose in the last 2 years • lower FEV_1 (grouped) • higher daily ICS dose	• low weight • daily use of OCS • low Baecke leisure scores • current non-use of theophylline • rib fractures	• low Baecke leisure index
Both spine and femur	• BMI>20 • younger age group • OCS use (or OCS dosage) in the last two years • lower FEV_1 (grouped)	• rib fractures	

§ See Table 55 to Table 58 on pages 131 to 134 for actual odds ratios

In addition, low BMD appears to be better predicted by risk factors than low spine BMD. From this data, we are not able to assess whether this is because spine BMD is more difficult to predict in general, or due to technical difficulties with measurement of BMD at the spine. The results above are consistent with current literature and understanding except for the increased risk in younger age groups. This is most likely an artefact of our sampling frame as discussed earlier – as younger people had to be at higher risk overall than older people to meet the study entry criteria. Theophylline has been used to treat respiratory diseases in the past, although it has fallen out of clinical usage. Theophylline use has been associated with low BMD in animal models.[235]

Where both men and women are included in the analysis together (see Table 55 to Table 58 – not listed in Table 58 above), the risk factors become "mixed", blurring the differences between genders. Overall, different mixes of risk factors predict low BMD in men and women, providing evidence that there are different factors contributing to low BMD in the different genders. While this is certainly interesting, at the practical level, physicians need to decide whether or not they should be referring their patients

with respiratory disease for densitometry, and considering different risk factors for different genders and anatomical sites (or even different bone density cutoffs or definitions) can unduly add a level of complexity to this decision. Therefore, if one set of risk factors for this one group of people with respiratory disease could be found which predicts who would benefit from densitometry, this would benefit patients. Therefore we return to discussion of the analysis for predicting BMD of Z<-1.5 at the spine or femur, in both men and women.

4.9 Discussion

Three of the four clinical risk factors constituting the final screening tool have previously been associated with low BMD in respiratory patients (low BMI,[71,70] poor lung function,[99] smoking[65,88]). Warfarin has been associated with low BMD in post-menopausal women only,[236] with warfarin use identified as a marker for other risk factors associated with low BMD eg poor health rather than low BMD alone.[236]

The specificity of our algorithm is poor (41%) at selected sensitivity of 86%. However, the specificity of other screening algorithms is also poor at the sensitivity they used. At sensitivity equal or greater than our target sensitivity of 90%, specificity was 13-51%, and area under the ROC curve was 0.7-0.81 in studies using SCORE,[190-195] and specificity was 25-48% and area under the ROC curve 0.73-0.79 for studies using non-SCORE prediction models.[60,73,85,198,196,195] Using "SCORE" to identify patients likely to have low BMD prior to DXA reduces the costs of screening programs by ~20% by identifying people with normal BMD not requiring bone densitometry.[237] This has significant cost-effectiveness implications. For further discussion of combining this risk factor analysis with other research, see Chapter 6 on page 178.

We did not collect all the information required to reliably estimate SCORE[190] or ORAI[238] in our patients eg rheumatoid arthritis status, current use of estrogen (as compared to HRT in a generic sense). Therefore, we have not generated estimates of SCORE or ORAI estimates for our cohort.

We would have liked to use half our data as a development and the second half as a validation cohort, much as some other authors have done.[238,239] However, these were much larger studies than ours (1279 and 1376 women) using nation-wide or multiple centres from which the sample was drawn. Therefore, we did not have a large enough sample size to attempt to validate the screening tool with our data.

However, our research group is in the process of preparing and submitting a manuscript to peer-reviewed journals using data collected in Newcastle, New South Wales in 1991-1993 by one of the study investigators[208] as a development cohort and using the data from this thesis as the validation cohort.

4.9.1 Discussion on why corticosteroid use and previous fractures did not feature prominently in analyses for predicting low BMD

It may also seem surprising that corticosteroid use and previous fractures did not appear to be good predictors of low BMD in this group. Corticosteroid usage may not be predictive of low BMD in this group if the participant had bone loss from corticosteroid usage prior to the last 2 years, as this would not have been picked up the questions used in the questionnaire if corticosteroid usage has varied over time (See discussion on page 89 in section 3.7.8 Study factor 20-22 – Number of courses of oral corticosteroids in the last 2 years.) However we did ask about fractures since age 40.

Fractures at the spine or ribs were of most interest to us given their high background prevalence in this patient group. Around 20% of the sample had experienced a bone fracture since age 40 (49/239), but the sites where participants sustained fractures varied. The total number of participants sustaining spine fractures was very small (N=4 - see Table 60), and may explain why spine fractures are so infrequently associated with low BMD in the previous analyses; whereas rib fractures are more common (N=20, see Table 61) and demonstrated better associations with low BMD in the previous analyses. The selection criteria used for this study was intended to select a higher risk group of participants for the study. However, as seen in Table 36, this group was not as high-risk as had been anticipated, with the mean BMD of all but one site was not significantly different to zero. Having a sample which was not as high risk as expected could explain why the number of fractures (particularly spine fractures) was so small.

Another possible explanation for the low numbers of spine fractures is that people with spine fractures would have been otherwise eligible for the study would also have been eligible to receive authority scripts for alendronate and therefore may have been excluded from the study because they were already taking alendronate. We recorded 25 people being unsuitable for the study for this reason. This represents 10% of the people excluded from the study who were alive. At the time this study

was recruiting alendronate was not widely prescribed and men were unable to obtain authority scripts for PBS-subsidised alendronate.

Table 60 – Spine fractures in participants with BMD of *Z*<-1.0, *Z* <-1.5 or *Z* <-2.0

	Total spine fractures	Spine BMD			Femur BMD			Spine or femur		
	N=	*Z*<-1.0	*Z*<-1.5	*Z*<-2.0	*Z*<-1.0	*Z*<-1.5	*Z*<-2.0	*Z*<-1.0	*Z*<-1.5	*Z*<-2.0
Males	2	1	1	0	2	2	0	2	2	0
Females	2	0	0	0	0	0	0	0	0	0
Total	4	1	1	0	2	2	0	2	2	0

Table 61 - Rib fractures in participants with BMD of *Z*<-1.0, *Z* <-1.5 or *Z* <-2.0

	Total rib fractures	Spine BMD			Femur BMD			Spine or femur		
	N=	*Z*<-1.0	*Z*<-1.5	*Z*<-2.0	*Z*<-1.0	*Z*<-1.5	*Z*<-2.0	*Z*<-1.0	*Z*<-1.5	*Z*<-2.0
Males	10	3	3	2	9	5	0	9	5	2
Females	10	2	0	0	3	2	2	4	2	0
Total	20	5	3	2	12	7	2	13	7	2

4.10 Study limitations

Case notes were used as the initial source of data. Therefore data on the initial eligibility of patients to participate in the study may be inaccurate. This may have resulted in patients who were eligible to participate in the study being excluded, although patients who were included in the first instance but in reality were not eligible to participate would have been excluded at a later stage in the recruiting.

Our exclusion criteria relating to alendronate contraindications (excluding patients with existing gastrointestinal disease) excluded more patients from the study than initially expected. The patients whom we excluded were in quite poor health, with numerous co-morbidities and risk factors for low BMD, and were therefore a high-risk group for low BMD.

We excluded patients who had been treated with alendronate or etidronate, because we intended to randomise patients subsequently found to have low BMD to daily alendronate in a randomised controlled trial. The active components of these drugs are retained in the body, changing BMD even after the tablets are discontinued,[240] and may therefore confound the results of the future randomised controlled trial. However, this also means that a high-risk group of patients has been excluded from the study, as many people already taking these drugs had vertebral fractures (which enabled them to be prescribed the drug at PBS-subsidised prices). The number of

patients to which this applies is small (10% of live subjects who did not meet all the criteria for entry to the study), but is still worthy of consideration

Our inclusion criteria were generous, resulting in the inclusion of larger numbers of participants than expected who were unlikely to have low BMD. In particular, allocating women two points if they were postmenopausal on the pre-screening questionnaire (Table 32 and Appendix 2) meant they needed few other risk factors for low BMD to be eligible for the study. Therefore the females on our study were at lower risk of having low BMD for their age than the men.

Our modest sample size makes drawing any conclusions from analyses of risk factors by gender or individual skeletal sites somewhat tenuous, although these have been presented for completeness.

4.11 Directions for future research

Future research could include studying risk factors on a larger sample size of participants, allowing more definitive conclusions to be drawn from analyses of relationships between low BMD and individual skeletal sites and genders, and investigation of the predictive value of these risk factors in other COPD populations. It would be useful to collect information on how many people had undergone densitometry prior to study entry, and to select higher-risk women, by not giving them additional points for being post-menopausal. Markers for co-morbidity other than warfarin could be considered.

Conclusion

Our sample was middle aged, with more men than women. Both men and women were overweight and sedentary compared to reference populations. Men and women had different patterns of risk factors, and the men had poorer health and lower age- and gender-matched BMD than the women. Individual risk factors that were associated with low BMD (with genders pooled) ($p<0.25$) were included in the multivariate analysis. At a p value of entry of 0.1, the multiple logistic regression "model" comprised three factors – having a body mass index <20, smoking >80 pack years of cigarettes, FEV_1 ≤60% predicted, and current use of warfarin. The combination of these four risk factors corresponded to a sensitivity of 86% and specificity of 41% and correctly classified 50% of patients. This was chosen in preference to an alternative model comprising 96% sensitivity and 21% specificity, which had a higher sensitivity but a poorer overall mix of sensitivity and specificity, correctly classifying only 36% of patients. The chosen model had a positive predictive value of 27%, and a negative predictive value of 92%, and had an area under the ROC curve (AUC) of 0.7. People who did not have any of the four risk factors in the multivariate logistic regression (comprising 65% of our sample) who had a risk of having $Z<-1.5$ of 13% or less would *not* be recommended for densitometry. The use of pre-screening questionnaires has the potential to reduce the cost of screening programs by ~20% by identifying subgroups who would not benefit from densitometry.

Chapter 5 - Methods and results for modelled estimates of number needed to screen and number needed to treat to prevent hip fractures over one and ten years with daily alendronate

This chapter investigates Aim 2 – Number needed to screen and number needed to treat

"Determine the number needed to treat (NNT) and number needed to screen for preventing hip fractures in nominated subgroups of the general population and the chronic obstructive airways population by treating with alendronate for one and ten years."

5.1 Number needed to treat

NNT was first described by Laupacis *et al.*[241] as a more meaningful tool for use in clinical practice than relative risks or odds ratios because it incorporates both the base-line level of risk and also the magnitude of the risk reduction. It is defined as "the number of people who need to be treated for a given duration to prevent one death or adverse event". NNT is the reciprocal of the absolute risk reduction (ARR), which is the difference between rates of adverse events, such as a fracture, in the control and intervention groups of randomised controlled trials. This is illustrated below:

$$NNT = \frac{1}{\frac{\text{number of events in control group}}{\text{number of people in control group}} - \frac{\text{number of events in intervention group}}{\text{number of people in intervention group}}} \quad [1]$$

$$= \frac{1}{ARR}$$

$$= \frac{1}{\text{control - intervention event rate}} \quad [2]$$

NNT is calculated for a specific patient group and for a particular period of time, and must always be considered within that context. NNT gives clinicians a tangible grasp of how effective the intervention is within these parameters.

NNT can easily be calculated by clinicians from information provided by drug companies such as the ARR. NNT is therefore a very useful tool for assisting clinicians to conceptualise the absolute risk of an adverse event that may occur if they do nothing, and the change in absolute risk that may be obtained by providing the patient with a particular intervention.

5.1.1 Clinical shortcomings of NNT

Laupacis *et al.*[241] summarised the clinical shortcomings of NNT, which result both from the properties of the measure and from the data used. NNT is an average of the number of patients requiring treatment in order to prevent one event. NNT gives no information regarding the fate of other patients who are treated in whom an adverse effect is not prevented. NNT estimates are developed from randomised controlled trials in which patients and conditions of treatment, levels of baseline risk, patient compliance, differ from regular clinical practice.

5.2 Number needed to screen

NNS was first described by Rembold *et al.*[242] as an extension to NNT, and is defined as the number of people needing to be screened to prevent one death or adverse event. It is intended for use as the basis of a strategy for disease screening and is calculated as follows:

$$\text{NNS} = \frac{\text{NNT}}{\text{Prevalence of disease}}$$

where "prevalence" is the rate of people with the disease of interest (using a designated definition) in a specified population at a specified time. The use of NNS also takes into account baseline risk, and allows more fair comparisons of screening strategies for diseases with different levels of baseline event rates.[242] NNS can also be calculated from clinical trials that directly test the benefit of a screening strategy (such as mammography for the prevention of breast cancer, or fecal occult blood testing for prevention of colon cancer), where the intervention is not a drug treatment but the screening strategy itself (See Table 70). The calculation of NNS in these trials is the same as the NNT formula (NNS=1/ARR). No such trials exist for preventing fractures with alendronate, therefore the use of the equation NNS=NNT/prevalence of disease will be used in the investigations presented in this thesis.

5.2.1 Clinical shortcomings of NNS

Additional errors are introduced into the NNS estimate by using prevalence estimates which do not come from the population from which the trial participants come, but use an estimates from a separate source eg data from another trial, or prevalence estimates from another setting or country. Limitations of applying trial data to actual clinical practice for NNT discussed above also apply to NNS regarding compliance with screening and treatment.

Providing that screening is useful, NNS provides a tangible guideline for busy clinicians to conceptualise the number of patients that need to be screened to prevent a fracture in patients that they see.

NNS will be further considered as part of the original research for this thesis.

5.3 From trial data to modelling

Data collected from randomised controlled trials provide us with useful information on the relative effectiveness of the treatment studied in the RCT, and on the safety and tolerability of the intervention (See Table 62). However, there are limitations in obtaining NNS and NNT estimates from RCT data. Long term studies on adverse events (eg fractures) are difficult to conduct, and results may not be available for a number of years. These trials may not include the sickest or least compliant patients who may have a different risk of hip fracture, death or institutionalisation. Thus, the effectiveness of the treatment in non-trial situations may be overestimated, thus altering NNS, NNT and cost-effectiveness estimates, and limiting generalisability of the findings of the study to other populations. The published reports of the RCT may often not include sufficient data regarding the population from which the study subjects were chosen to estimate NNS except in a very broad sense, which may be so broad that the estimate is useless.

The sample of patients in the RCT's may not be representative of the underlying population. This may be related to differences in inclusion and exclusion criteria, and different definitions of low bone density - such as the World Health Organisation definition (*T*-score <-2.5), or "established osteoporosis" (presence of existing fractures) or the Medicare definition (*Z*-score of <-1.5), or even a novel definition used for the purpose of the individual trial. Therefore, the shape of the underlying statistical distribution of the trial population may be unknown, although likely to be significantly different from normal, with sections of the normal population under- and over-represented. This means that individual trials may not be able to be sensibly compared to each other.

However, modelling these scenarios provides information for today, and allows the possibility of exploring scenarios such as what happens when different subgroups of the population are screened and treated, using simulated populations with known characteristics.

Table 62– Characteristics of study populations of randomised controlled trials of alendronate (10mg/day) versus placebo

Study	Black, 1996[243]	Cummings, 1998[244]	McClung, 1998[245]	Liberman, 1995[145]	Orwoll, 2000[246]	Saag, 1998[109]
Age range Gender	55-81 Female	54-81 Female	40-59 Female	45-80 Female	31-87 Male	17-83 Male & female
Inclusion criteria	Existing vertebral #, NOF *T*<-1.6 (0.68 g/cm2), post-menopausal >2 years	no vert #, NOF *T*<-1.6 (0.68 g/cm2), postmenopausal >2 years	Healthy women 6-36 months post menopause, -2<*T*<+2, no vertebral #	LS *T*<-2.5 & 5 years post-menopause	NOF *T*<-2 AND LS *T*<-1 OR NOF *T*<-1 AND (vertebral deformities OR previous #) with low serum testosterone	Require >1 year OCS of 7.5mg/day prednisolone
Exclusion criteria	Uncontrolled disease, no current treatment for osteoporosis, no GI ulcers	Uncontrolled disease, no current treatment for osteoporosis, no GI ulcers	no #, no disorders/ treatment affecting bone/mineral metabolism, no GI problems	no disorders/ treatment affecting bone/mineral metabolism	any prior treatment for osteoporosis, cancer, oesophageal problems	Non-osteoporotic metabolic bone disease , low serum vitamin D, use of non-HRT osteoporosis drugs, other severe disease
Trial duration *n* PLACEBO (C) *n* alendronate (I) Average starting age Initial NOF BMD Initial LS BMD	3 years 1005 1022 70.85±5.6 0.565±0.07 0.79±0.14	4 years 2218 2214 67.65±6.2 0.593±0.06 0.842±0.13	3 years 90 88 51.7±0.4 0.93±0.01	3 years 397 597 64 0.675 0.815	2 years 95 146 63±12.5 (*T*-score) -2.25 (*T*-score) -2.05	1 year 159 157 55 0.94
% change in NOF BMD from baseline	4.1%	3.0%	6.22%	5.9±0.5%	2.60%	2.20%
% change in LS BMD from baseline	6.2%	6.8%	7.5%	8.8±0.4%	5.30%	3.30%
Hip ARR (C-I) Hip RRR (C-I/C) Hip NNT	1.1% 51% 90	0.22% 21% 447		0.59% 78% 170		
Prevalence estimate Hip NNS	9.18% 979	41% 1,083	50% - 75%	0.99% - 16.85% 1009 - 18891	2.22% - 12.30% 0.7%	 2.3%
LS ARR (C-I) LS RRR (C-I/C) LS NNT LS NNS	2.7% 55% 37 400	1.6% 45% 64 154		2.7% 49% 37 220 - 3749	6.7% 91% 15 121 - 673	1.5% 40% 68

5.4 Methods – modelled estimates of NNS and NNT

Aim 2 will be investigated by the development of a spreadsheet-based "model" to simulate the NNS and NNS for treating subgroups of the general population and people with moderate to severe respiratory disease with alendronate for a specified period of time. Since some authors have proposed that treatment for reduced bone density should begin at *Z*-scores other than <-1.5[247,226], modelling estimates for *Z*<-1.0 and *Z*<-2.0 as well as <-1.5 have been included.

5.4 Model inputs

- Lunar reference data for the mean BMD and standard deviations for age and gender[217] (See Table 77 in Appendix 4 on page 197).
- Reducing BMD by 1 SD increases the relative risk of a hip fracture by 2.6x.[57]
- Australian population hip fracture rates, derived from fracture incidence data; and Australian population estimates from the 1996 Census of Population and Housing.[54] Hip fracture incidence data by age and gender was obtained by request from the Australian Institute of Health and Welfare (see Appendix 5 – Hip fracture incidence in Table 78, page 198).
- Hip fracture rates for treated and non-treated groups – developed from equations in Kanis *et al.*[1] See Equation 1 and Equation 2.

Equation 1 and Equation 2 calculate the rate of hip fracture below (Equation 1) or at (Equation 2) a stationary point on the Normal distribution, defined by the mean and standard deviation of a given age and gender group. These pre and post hip fracture rates are used to calculate the effect of treatment for the NNT and NNS.

Equation 1 - The pre-treatment fracture rate for the risk of fracture in the short perspective (not accounting for deaths) for those BELOW the threshold for BMD (*g*)

= Yearly incidence (of fracture) of the age group x

$\Phi((g - \mu)/\sigma) + \log(RR)/ ((g - \mu)/\sigma)$

Equation 2 - The pre-treatment fracture rate for the risk of fracture in the short perspective (not accounting for deaths) for those AT the threshold for BMD (*g*)

= Yearly incidence (of fracture) of the age group x

$$\exp\left(-\log(RR)\,(x - \mu)/\sigma - \frac{(\log(RR))^2}{2}\right)$$

where :

μ	Is the mean
σ	Is the standard deviation of BMD at the current age
RR	Relative risk of (hip) fracture for decreasing BMD by 1SD (= 2.6)
log (RR)	Is the e-log of the risk ratio of an individual with BMD 1 SD below another individual
Φ	normal distribution function (mean=0, SD=1)
g	Threshold BMD (BMD below where treatment begins)

For worked examples see Appendix 6 on page 199.

5.6 *Creating the simulation model*

We used Microsoft Excel 97 (Microsoft Corporation) to calculate the hip fracture rates using Equation 1 and Equation 2 (from Kanis *et al.*[1]). This method of obtaining pre-treatment hip fracture rates was validated with the data in the original paper using the NHANES reference data,[11] and the Australian hip fracture data (from Australian Institute of Health and Welfare hip fracture data (Table 78), and from ABS Census data[54]) to ensure that no errors had been made in the transfer of the formula to Microsoft Excel 97.

5.7 *Modelling effect of COPD*

To model the effect of COPD, the shape and distribution of the COPD population, and the position of the curve of the COPD population relative to the general population needs to be able to be described.

5.7.1 Position of the COPD population relative to the normal population

Patients with COPD have a lower mean BMD than the general population, with an estimated average 10% reduction in mean BMD compared to controls.[4]

To simulate the effect of having COPD, the shape of the curve and the placement of the mean BMD for the COPD population need to be determined.

The standard deviation of the COPD population is assumed to be identical to that used for the general population pre-treatment (0.12 g/cm^2 in women, and 0.13 g/cm^2 in men) in the absence of data to the contrary.

5.7.2 Shape of the curve for the COPD distribution

Data on the distribution of the COPD population was required to estimate hip fracture rates in this population, however no published data is available on the shape of the distribution of the COPD population.

Data from the cohort of patients studied by us to develop a screening tool for identifying patients who did not require bone densitometry (investigated as part of this thesis) are described in Chapter 4.3.1 - Table 36 on page 100). The patient data from this cohort was assessed by gender, and anatomical site (lumbar spine (L2-L4), neck of femur, and total femur) to determine if the distributions were significantly non-Normal. For modelling purposes, it will be assumed that the COPD population is Normally distributed.

5.7.3 Estimation of the mean BMD for the COPD population

Literature estimates of BMD reduction conferred by having COPD are around 10%[4] (approximately one standard deviation). A sensitivity analysis on varying this by up to ±100% is shown in Table 63.

If the COPD effect is underestimated, the prevalence of low BMD and the fracture rate in the Z<-1.5 group will also be underestimated, and the NNS estimates after one and ten years and the NNT estimates after one year of daily alendronate treatment will be less. The NNT after ten years of daily alendronate treatment will remain unchanged.

If the COPD effect is overestimated, the prevalence of low BMD and the fracture rate in the Z<-1.5 group will also be overestimated, and the NNS estimates after one and ten years, and the NNT estimates after one year of daily alendronate treatment will be higher, having moved closer to NNS and NNT estimates for the general population. NNT estimates after ten years of daily alendronate treatment would remain unchanged.

Table 63 – Effect of changing the COPD effect from 10% in women aged 55-75 with COPD and bone density of *Z*<-1.5 on number needed to screen and number needed to treat estimates for 1 and 10 years

NNS for treating women with COPD and *Z*<-1.5 with alendronate for 1 year							
Effect of COPD	0%	5%	9%	10%	11%	15%	20%
% change from 10%	-100%	-50%	-10%	0%	+10%	+50%	+100%
55 years	24,479	12,275	7,562	6,758	6,060	4,042	2,594
65 years	6,105	3,218	2,045	1,840	1,661	1,132	743
75 years	1,301	714	466	422	382	266	178
NNT for treating women with COPD and *Z*<-1.5 with alendronate for 1 year							
Effect of COPD	0%	5%	9%	10%	11%	15%	20%
% change from 10%	-100%	-50%	-10%	0%	+10%	+50%	+100%
55 years	1,635	1,579	1,517	1,499	1,481	1,395	1,264
65 years	408	396	384	380	376	358	331
75 years	87	85	83	82	81	78	73
NNS for treating women with COPD and *Z*<-1.5 with alendronate for 10 years							
Effect of COPD	0%	5%	9%	10%	11%	15%	20%
% change from 10%	-100%	-50%	-10%	0%	+10%	+50%	+100%
55 years	1,700	891	565	508	458	311	203
65 years	477	271	181	165	150	107	73
75 years	147	82	55	50	46	33	23
NNT for treating women with COPD and *Z*<-1.5 with alendronate for 10 years							
Effect of COPD	0%	5%	9%	10%	11%	15%	20%
% change from 10%	-100%	-50%	-10%	0%	+10%	+50%	+100%
55 years	112	113	112	111	111	106	98
65 years	32	33	34	34	34	34	32
75 years	1.2	1.1	1.1	1.1	1.1	1.0	0.9

Therefore, the COPD population will be simulated by:

- reducing the mean BMD to 10% below that of the general population for age and gender
- maintaining the standard deviation equal to that of the pre-treated general population
- assuming a Normal distribution

g (threshold BMD, the BMD value below which people receive treatment) will remain constant but the proportion of the COPD population below *g* will be larger than the proportion of the general population below *g*.

If the "true" COPD effect is different to 10%, the NNS and NNT estimates may be under- or over-estimated.

5.8 Modelling the effect of treatment

Alendronate treatment increases BMD of the neck of femur by approximately 5% in postmenopausal women (See Table 62). The model assumes that the effect of treatment is the same regardless of initial bone density (See Chapter 5.9). A sensitivity analysis on varying the 5% change in BMD by ±100% are listed in Table 64.

If the "true" effectiveness of daily alendronate treatment is greater than 5%, then fracture rates will be even more reduced in people receiving treatment, and NNS and NNT estimates after one and ten years will be reduced.

Conversely, if the "true' effectiveness of daily alendronate is less than 5%, then treatment will have little effect, as fracture rates in the people receiving treatment will become similar to fracture rates in people receiving placebo. Therefore, NNS and NNT estimates after one and ten years of treatment will increase.

Table 64 – Effect of changing treatment effect from 5% in women in the general population commencing treatment at age 55, 65, and 75 years with bone density of *Z*<-1.5.

NNS for treating women in the general population at *Z*<-1.5 with alendronate for 1 year						
Treatment effect	2.5%	4.5%	5%	5.5%	7.5%	10%
Change from 5%	-50%	-10%		+10%	+50%	+100%
55 years	45,020	26,752	24,479	22,623	17,701	14,364
65 years	11,293	6,680	6,105	5,636	4,391	3,545
75 years	2,417	1,424	1,301	1,200	931	749
NNT for treating women in the general population at *Z*<-1.5 with alendronate for 1 year						
Treatment effect	2.5%	4.5%	5%	5.5%	7.5%	10%
Change from 5%	-50%	-10%		+10%	+50%	+100%
55 years	3,008	1,787	1,635	1,511	1,183	960
65 years	754	446	408	377	293	237
75 years	161	95	87	80	62	50
NNS for treating women in the general population at *Z*<-1.5 with alendronate for 10 years						
Treatment effect	2.5%	4.5%	5%	5.5%	7.5%	10%
Change from 5%	-50%	-10%		+10%	+50%	+100%
55 years	3,010	1,794	1,642	1,518	1,187	962
65 years	785	478	438	405	317	257
75 years	173	120	112	105	85	71
NNT for treating women in the general population at *Z*<-1.5 with alendronate for 10 years						
Treatment effect	2.5%	4.5%	5%	5.5%	7.5%	10%
Change from 5%	-50%	-10%		+10%	+50%	+100%
55 years	201	120	110	101	79	64
65 years	52	31	29	27	21	17
75 years	4	3	3	2	2	2

Therefore, the size of the treatment effect is important, and data on the effect of alendronate on BMD over longer periods of time will enable the treatment effect to be estimated more accurately.

The effect of treatment will be simulated by:

- Increasing the population mean BMD by 5%
- maintaining the standard deviation equal to that of the pre-treated population

The same position on the Normal curve will be associated with a lower hip fracture rate post-treatment.

If the "true" effect of treatment is different to 5%, the NNS and NNT estimates for one and ten years of treatment with daily alendronate will be over- or under-estimated.

5.9 Other model assumptions:

- All persons are screened (the model uses N=1000 for the size of the screened population for each age)
- All persons in assigned treatment group are treated, with levels of compliance assumed to be equal to that in the RCT's of alendronate from which the effect of treatment is derived (See the list of trials in Table 62).
- All persons at any point in the normal distribution receive the same increase in BMD due to treatment
- For comparative purposes, the population mean is used regardless of whether the general population or the COPD population is being considered.
- The prevalence of low bone density in the group treated (eg Z =–1 to Z=–2) is equivalent to the probability assigned to each Z-score group by the use of normal distributions.

Therefore, out of the 1000 patients screened, 158.7 patients in the general population are treated in the treatment group Z<-1.0 (15.87%), 66.8 in Z<-1.5 (6.68%), and 22.8 in Z<-2.0 (2.28%) (See Table 65). For the COPD population, the numbers are as follows, depending on gender and age: 359 – 396 for Z<-1.0 (35.9 – 39.6%), 195 – 222 for Z<-1.5 (19.5 – 22.2%), and 87 – 103 for Z<-2.0 (8.7 – 10.3%) (See Table 66). This is the proportion of people with the corresponding Z-scores in the general and COPD populations. The number treated in a particular Z-score

group is constant in the general population (See Table 65), but changes in the COPD population (See Table 65). See Chapter Chapter 6.1.4 on page 168 for further discussion of this phenomena.

Therefore, as the population ages, hip fracture rates increase – for the whole population and for each *Z*-score group described. As the hip fracture rate increases, so do the number of hip fractures prevented.

The validity of these assumptions are discussed further in Chapter 6.

Table 65 – Hip fracture rates and number of hip fractures prevented after one year for men and women in the general population, for the whole population and subgroups of people with BMD Z<-1.0, Z<-1.5, and Z<-2.0

Females	Whole population	Z<-1.0			Z<-1.5			Z<-2.0		
	Hip fracture rate (per 1000)	Hip fracture rate (per 1000)	Hip fractures prevented	Number of people treated	Hip fracture rate (per 1000)	Hip fractures prevented	Number of people treated	Hip fracture rate (per 1000)	Hip fractures prevented	Number of people treated
55 to 59	0.05	0.47	0.07	158.7	2.07	0.04	66.8	3.07	0.02	22.8
60 to 64	0.10	1.01	0.01	(15.87%	4.44	0.01	(6.68%	6.59	0.00	(=2.28%
65 to 69	0.20	2.01	0.03	of 1000)	8.82	0.02	of 1000)	13.09	0.01	of 1000)
70 to 74	0.43	4.29	0.05		18.81	0.03		27.93	0.02	
75 to 79	1.00	9.97	0.13		43.73	0.08		64.91	0.04	
80 to 84	1.96	19.64	0.25		86.13	0.15		127.85	0.08	
85+	3.92	39.18	0.50		171.88	0.30		255.13	0.15	
Males	Whole population		Z<-1.0			Z<-1.5			Z<-2.0	
Commence treatment at age	Hip fracture rate (per 1000)	Hip fracture rate (per 1000)	Hip fractures prevented	Number of people treated	Hip fracture rate (per 1000)	Hip fractures prevented	Number of people treated	Hip fracture rate (per 1000)	Hip fractures prevented	Number of people treated
55 to 59	0.19	0.58	0.03	158.7	0.84	0.00	66.8	1.24	0.01	22.8
60 to 64	0.29	0.88	0.00	(=15.87%	1.27	0.00	(=6.68%	1.89	0.01	(=2.28%
65 to 69	0.69	2.1	0.01	of 1000)	3.03	0.01	of 1000)	4.49	0.02	of 1000)
70 to 74	1.41	4.28	0.02		6.18	0.01		9.18	0.04	
75 to 79	3.29	9.99	0.04		14.42	0.03		21.4	0.09	
80 to 84	6.67	20.27	0.09		29.25	0.05		43.42	0.18	
85+	14.65	44.54	0.19		64.27	0.12		95.4	0.39	

Table 66 - Hip fracture rates and number of hip fractures prevented after one year for men and women in the COPD population, for the whole population and subgroups of people with BMD *Z*<-1.0, *Z*<-1.5, and *Z*<-2.0

COPD females	Whole population	Z<-1.0			Z<-1.5			Z<-2.0		
Age	Hip fracture rate (per 1000)	Hip fracture rate (per 1000)	Number of hip fractures prevented	Number of people treated	Hip fracture rate (per 1000)	Number of hip fractures prevented	Number of people treated	Hip fracture rate (per 1000)	Number of hip fractures prevented	Number of people treated
55 to 59	0.95	1.82	0.19	395	2.46	0.15	222	3.50	0.10	103
60 to 64	1.99	3.86	0.39	385	5.25	0.30	214	7.47	0.19	98
65 to 69	3.86	7.59	0.72	375	10.35	0.54	207	14.75	0.35	94
70 to 74	7.9	15.92	1.37	359	21.82	1.02	195	31.19	0.65	87
75 to 79	18.36	37.01	3.19	359	50.72	2.37	195	72.49	1.51	87
80 to 84	36.17	72.91	6.29	359	99.90	4.67	195	142.78	2.98	87
85+	72.17	145.49	12.55	359	199.35	9.32	195	284.92	5.94	87
COPD males	Whole population	Z<-1.0			Z<-1.5			Z<-2.0		
Age	Hip fracture rate (per 1000)	Hip fracture rate (per 1000)	Number of hip fractures prevented	Number of people treated	Hip fracture rate (per 1000)	Number of hip fractures prevented	Number of people treated	Hip fracture rate (per 1000)	Number of hip fractures prevented	Number of people treated
55 to 59	0.39	0.74	0.08	396	1.00	0.06	222	1.42	0.04	103
60 to 64	0.58	1.11	0.11	389	1.51	0.09	217	2.15	0.06	100
65 to 69	1.35	2.62	0.26	382	3.57	0.20	212	5.08	0.13	97
70 to 74	2.68	5.30	0.50	372	7.24	0.37	204	10.32	0.24	92
75 to 79	6.26	12.37	1.16	372	16.89	0.87	204	24.07	0.56	92
80 to 84	12.69	25.09	2.35	372	34.26	1.76	204	48.84	1.14	92
85+	27.89	55.12	5.16	372	75.27	3.87	204	107.31	2.49	92

5.10 Extension of model beyond the short term

The equations for the risk of hip fracture used in this model[1] calculate hip fracture risk for the short term only. However, treatment with alendronate continues to increase BMD and reduce fracture risk over time with treatment up to 7 years in post-menopausal women,[240] and few people would take alendronate for only one year. Therefore, we incorporated a Markov model as an extension to the 1-year model, which allowed us to calculate risk of hip fracture over time, and therefore NNS and NNT over a longer period of time.

5.11 Markov model

A Markov model was developed concerning the specification of relationships between the probability of hip fracture, death and institutionalisation for different gender, age, BMD, BMD threshold for treatment, patients' treatment status (general population or COPD) to enable estimates of cost-effectiveness to be made, including estimates of NNS and NNT beyond one year. The Markov model begins with probabilities that an individual will sustain a hip fracture, die, be institutionalised, or remain healthy over that year. The model "iterates" for every year, beginning with the likelihood of the event from the end of the previous year.

The assumptions for the Markov section of the model are as follows and are obtained from literature data, or from expert opinion where no literature data is available. Events occur at the end of each year, and each person has a defined risk of experiencing the following each year:

- hip fracture
- admittance to an institution (nursing home)
- death

After a hip fracture, an individual has a higher risk of being admitted to an institution or dying.[47,46] Patients admitted to a nursing home cease being allocated to a treatment group (and are no longer prescribed tablets), because there are too many uncertainties about the risk of hip fracture once a patient is institutionalised to allow hip fracture risk to be accurately estimated. This is discussed further in Chapter 6.1.3 on page 168. Therefore, as far as treatment is concerned, people drop out of the model as if they have died.

Extending the model beyond one year requires additional data on rates of institution and death,[248,46,202] and prevalence of COPD in the general population,[56] The rates of mortality and institutionalisation (both in general and following hip fractures) are listed in Table 67. We have assumed that the mortality rates (in general and after hip fracture), and institutionalisation rates in people with COPD are double that experienced by the general population, since there is no data on the topic. Should the estimates be too high, with the "true" rate of deaths and institutionalisations closer to that of the general population, the NNS and NNT estimates after 10 years may be closer to estimates for the general population than those presented for the COPD population. However, until such time as accurate estimates are available, more accurate assessments can not be made.

Data from previous versions of the Markov model have been presented at scientific conferences.[249,250]

Table 67 – Model input - rates of hip fracture, mortality, and institutionalisation (in general and following hip fractures) by age group and COPD status†

	Hip fracture rate per 100[10]		Mortality rate (%)		Mortality rate from hip fracture			Institutionalisation rate – general		Institutionalisation rate - as a result of hip fracture[46]
Age	Females	Males	POP[202]	COPD	POP[47]	COPD	Institutionalised[47]	POP[248]	COPD	All
55 to 59	0.0471	0.0191	0.46%	0.91%	9%	18%	50%	0.16%	0.31%	11%
60 to 64	0.1012	0.0290	0.73%	1.45%	13%	26%	50%	0.16%	0.31%	12%
65 to 69	0.2011	0.0690	1.20%	2.41%	13%	26%	50%	0.29%	0.57%	12%
70 to 74	0.4289	0.1410	2.03%	4.06%	27%	54%	50%	0.71%	1.41%	19%
75 to 79	0.9969	0.3287	3.53%	7.06%	27%	54%	50%	1.63%	3.25%	19%
80 to 84	1.9636	0.6668	6.36%	12.72%	33%	66%	50%	3.82%	7.64%	31%
85+	3.9184	1.4652	15.0%	30.00%	33%	66%	50%	7.79%	15.58%	31%

† Mortality rates are identical for males and females, either in the general population (POP) or with COPD. Mortality rates from institutionalisation are identical for the general population and the COPD population.

5.12 Calculating NNT

NNS and NNT estimates from the model are calculated from comparing groups allocated to treatment before and after treatment takes place. These simulate the control and intervention arms of a RCT and are algebraically equivalent to standard epidemiological formulae listed earlier as follows:

$$\text{NNT} = \frac{1}{\frac{\text{number of events in control group}}{\text{number of people in control group}} - \frac{\text{number of events in intervention group}}{\text{number of people in intervention group}}}$$

$$= \frac{1}{\frac{\text{number of events in control group} - \text{number of events in intervention group}}{\text{number treated}}}$$

$$= \frac{\text{number treated}}{\text{number of events in control group} - \text{number of events in intervention group}}$$

$$= \frac{\text{number treated}}{\text{number of hip fractures prevented}} = \text{NNT used in model}$$

5.13 Calculating NNS estimates

NNS estimates are calculated by using the following formulae, which are algebraically equivalent to the formula for NNS as published by Rembold *et al.*[242] (See page 142).

$$\text{NNS} = \frac{\text{NNT}}{\text{Prevalence of disease}}$$

$$= \frac{1}{\frac{\text{number of hip fractures prevented}}{\text{number of people treated}} \div \frac{\text{number of people with disease}}{\text{number of people in population}}}$$

$$= \frac{1}{\text{hip fracture prevented}} \times \frac{\text{number of people screened}}{\text{number of people treated}}$$

$$= \frac{\text{number of people screened}}{\text{number of hip fractures prevented}}$$

= NNS equation used in model

Prevalence of the disease at the threshold BMD *g* is calculated by determining the percentage of the normal population below *g*.

5.14 Results - NNT and NNS estimates

5.14.1 NNS and NNT estimates for treating patients in the general population and patients with COPD for 1 year

Estimates for NNT and NNS for preventing fractures over 1 year are listed in Table 68.

Table 68 – Modelled estimates of NNS and NNT for screening females and males aged 55, 65 and 75 years, to treat patients with bone density of *Z*<-1.0, *Z*<-1.5, *Z*<-2.0 or *T*<-2.5 with daily alendronate for 1 year

		General Population				COPD			
Start treatment at age	treatment decision (*Z*-score)‡	NNS	NNT	% in group treated	% of all hip fractures in the population	NNS	NNT	% in group treated	% of all hip fractures in the population
Females									
55	<-1	14,875	2,360	16%	48%	5,150	2,035	40%	75%
	<-1.5	24,479	1,635	7%	29%	6,758	1,499	22%	56%
	<-2	48,428	1,102	2%	15%	10,279	1,057	10%	38%
65	<-1	3,710	589	16%	48%	1,383	519	38%	74%
	<-1.5	6,105	408	7%	29%	1,840	380	21%	56%
	<-2	12,079	275	2%	15%	2,848	267	9%	36%
75	<-1	790	125	16%	48%	313	112	36%	72%
	<-1.5	1,301	87	7%	29%	422	82	20%	56%
	<-2	2,573	59	2%	15%	662	57	9%	34%
Males									
55	<-1	36,672	5,818	16%	48%	12,675	5,015	40%	76%
	<-1.5	60,379	4,032	7%	29%	16,637	3,695	22%	56%
	<-2	119,392	2,716	2%	15%	25,281	2,604	10%	38%
65	<-1	10,583	1,679	16%	48%	3,848	1,469	38%	74%
	<-1.5	17,415	1,163	7%	29%	5,096	1,079	21%	56%
	<-2	34,454	784	2%	15%	7,841	758	10%	36%
75	<-1	2,292	364	16%	48%	864	321	37%	74%
	<-1.5	3,772	252	7%	29%	1,152	235	20%	56%
	<-2	7,462	170	2%	15%	1,787	165	9%	36%
BMD *T*<-2.5 Females (0.680 g/cm^2)									
55	-1.68	30,407	1,428	5%	24%	7,684	1,332	17%	51%
65	-1.15	4,231	529	13%	42%	1,486	475	32%	69%
75	-0.73	645	151	23%	59%	281	131	47%	81%
BMD *T*<-2.5 Males (0.750 g/cm^2)									
55	-1.58	66,828	3,778	6%	26%	17,650	3,493	19%	54%
65	-1.22	12,936	1,431	11%	39%	4,290	1,288	30%	67%
75	-0.97	2,235	371	17%	49%	852	327	38%	74%

‡ "Treatment decision" is the *Z*-score (standardised for age and gender) at which the general population or the COPD population (who have all been screened) are treated. Also known in the original paper (Kanis *et al.* 2000[1]) as *g*.

5.14.2 NNS and NNT estimates for treating patients in the general population and patients with COPD for 10 years

The number needed to screen and treat for 10 years are summarised in Table 69, with the data for NNS and NNT estimates after 10 years as a comparison. Data for NNS and NNT for treatment for 10 years in the group of patients beginning treatment at age 75 has not been tabulated because we consider that these estimates are not robust at such an advanced age. See Chapter 6 for further discussion on this idea.

The most useful aspect of using modelling to estimate NNS and NNT is that mortality and institutionalisation rates are factored in, making the estimates more realistic. The extent to which the 10 year NNS and NNT figures obtained from the Markov simulation take into account deaths and institutionalisation rates is also illustrated in Table 69. Further discussion on this idea can be found in Chapter 6.1.4 on page 169.

The hip fractures prevented after one year and after ten years are indicated in separate columns. The NNS and NNT estimates for ten years (using cumulative hip fractures prevented) are not adjusted for mortality or institutionalisations. These have been compared to the NNS and NNT estimates obtained using the Markov simulations (which *do* include mortality and institutionalisations).

Table 69 – Modelled estimates of NNS and NNT for screening females and males aged 55, 65 and 75 years, to treat patients with bone density of *Z*<-1.0, *Z*<-1.5, *Z*<-2.0 or *T*<-2.5 with daily alendronate for 1 and 10 years

		General Population								COPD							
FEMALES		1 year		10 years (includes Markov simulation)		10 years (using cumulative hip fractures prevented)		Ratio of cumulative model to Markov simulation		1 year		10 years (includes Markov simulation)		10 years (using cumulative hip fractures prevented)		Ratio of cumulative model to Markov simulation	
Start treatment at age	Treatment decision (Z-score)	NNS	NNT	NNS	NNT	NNS	NNT	NNS	NNT	NNS	NNT	NNS	NNT	NNS	NNT	NNS	NNT
55	<-1	14,875	2,360	999	159	694	110	0.69	0.69	5,150	2,035	381	149	251	99	0.66	0.67
	<-1.5	24,479	1,635	1,642	110	1,142	76	0.70	0.70	6,758	1,499	508	111	333	74	0.66	0.66
	<-2	48,428	1,102	3,242	74	2,259	51	0.70	0.70	10,279	1,057	787	80	511	53	0.65	0.66
65	<-1	3,710	589	268	42	165	26	0.61	0.62	1,383	519	122	46	65	24	0.53	0.53
	<-1.5	6,105	408	438	29	272	18	0.62	0.63	1,840	380	165	34	87	18	0.53	0.53
	<-2	12,079	275	853	19	537	12	0.63	0.64	2,848	267	259	24	136	13	0.53	0.53
75	<-1	790	125	-	-	-	-	-	-	313	112	-	-	-	-	-	-
	<-1.5	1,301	87	-	-	-	-	-	-	422	82	-	-	-	-	-	-
	<-2	2,573	59	-	-	-	-	-	-	662	57	-	-	-	-	-	-
MALES																	
55	<-1	36,672	5,818	3,044	483	2,111	335	0.69	0.69	12,675	5,015	1,126	441	752	298	0.67	0.68
	<-1.5	60,349	4,032	5,008	335	3,473	232	0.69	0.69	16,627	3,695	1,492	328	993	221	0.67	0.67
	<-2	119,392	2,716	9,900	225	6,871	156	0.69	0.69	25,281	2,604	2,297	234	1,520	157	0.66	0.67
65	<-1	10,583	1,679	777	122	478	76	0.61	0.62	3,848	1,469	328	125	179	68	0.55	0.55
	<-1.5	17,415	1,163	1,276	84	787	53	0.62	0.62	5,096	1,079	440	93	239	51	0.54	0.54
	<-2	34,454	784	2,512	56	1,556	35	0.62	0.63	7,841	758	687	66	370	36	0.54	0.54
75	<-1	2,292	364	-	-	-	-	-	-	864	321	-	-	-	-	-	-
	<-1.5	3,772	252	-	-	-	-	-	-	1,152	235	-	-	-	-	-	-
	<-2	7,462	170	-	-	-	-	-	-	1,787	165	-	-	-	-	-	-

5.15 Summary of NNT and NNS findings

If the *Z*-score at which patients are treated decreases:

- NNT decreases
- NNS increases.

as the underlying hip fracture rate increases

If BMD (in g/cm^2) is held constant, as age increases:

- NNT decreases
- NNS decreases

as the underlying hip fracture rate increases

The likelihood (prevalence) of having a *T*-score less than a given value (eg *T*<-2.5) increases with age as the underlying hip fracture rate increases.

(NB The underlying hip fracture rate increases with advancing age – this is input into the model.)

5.15.1 Which groups have the lowest NNS estimates?

NNS estimates are lowest in the high *Z*-score groups eg *Z*<-1.0. This is due to the low disease prevalence in the high *Z*-score groups where there are fewer numbers of hip fractures to be prevented by the treatment.

5.15.2 Which groups have the lowest NNT estimates?

NNT is lowest in the women, in the lowest standard deviation scores and the oldest age groups where the effect of treatment and the fracture risk is highest.

5.15.3 Comparison of the general population and the COPD population

If people of a given age and gender are treated in either the general population or the COPD population, both groups will have similar NNT (similar underlying hip fracture rate), but the COPD group will have lower NNS (higher prevalence of reduced BMD).

5.15.4 Comparison of men and women

Men have lower underlying rate of hip fracture than females at a given age and *Z*-score, and therefore higher NNS and NNT.

Conclusion

Using literature equations and Markov simulations, approximately 6100 65 year old women in the general population with BMD of *Z*<-1.5 need to be screened and 408 need to be treated to prevent one hip fracture with daily alendronate treatment for one year.

For ten years of daily alendronate treatment (taking account of hip fractures, institutionalisations and deaths which occur over the ten year period), approximately 430 of these women would need to be screened and 29 treated to prevent one hip fracture.

Approximately 1840 65 year old women in the COPD population with BMD *Z*<-1.5 need to be screened and 380 need to be treated to prevent one hip fracture with daily alendronate treatment for one year. For ten years of daily alendronate treatment, approximately 165 of these women would need to be screened and 34 treated to prevent one hip fracture.

Number needed to screen decreases with increasing disease prevalence.

Number needed to treat decreases as hip fracture rates increase.

Chapter 6 – Discussion of modelled estimates of number needed to screen and number needed to treat to prevent hip fractures over one and ten years with daily alendronate

6.1 Challenges to model inputs

6.1.1 Choice of fracture type

There are many sites at which bones can fracture. We have chosen to focus on hip fractures for the following reasons:

Morbidity after hip fractures is high,[251] but there is no excess mortality after vertebral fracture.[252] Part of this may be due to the age distribution of hip and vertebral fractures, with hip fractures common in the very elderly, and vertebral fractures more commonly occurring at a younger age.[252,253]

Hip fractures nearly always result in hospitalisation,[254] and are therefore easier to study in an epidemiological context than fractures of the ribs or vertebra, which are asymptomatic in a high proportion of cases and therefore under-diagnosed in the short term.[51,52]

In the COPD population, fractures of the vertebra and rib are common.[255,256] This would be an argument for using these fractures instead of, in addition to hip fractures, or indeed using all fractures. However, using only one type of fracture that is able to be easily identified in epidemiological terms is also a good place to begin economic analysis as the scenarios required for modelling are less complex.

6.1.2 Choice of data source for hip fractures

We have chosen to use data from centralised Commonwealth sources[257] (See Table 78). There have been no population based studies of hip fracture incidence in South Australia, although there have been several others in Australia – in Dubbo,[51] Geelong[51,52] Tasmania[53] and Western Australia.[258] There is geographical variation within Australia,[53] and therefore using Australia-wide data may not be readily generalisable to Adelaide. While this is a valid comment, we were not able to obtain any more valid data for our region than from hospital separations, and this data will be able to be generalised to Australia as a whole, but with the known geographic variation we must expect some variation from the average data in individual regions.

6.2 Challenges to model assumptions

6.2.1 Assumption of 100% compliance with screening

This model assumes that all patients of the selected gender aged 55, 65 or 75 have a screening DXA. This assumption is unlikely to be fulfilled in reality. However, the next best assumption to make in the real world may be that a random selection of patients (which would approximate a representative sample of the entire population of that gender and age). Or, is it a more correct assumption to make that the patients presenting for screening would not be a representative sample? In reality, screening could be either:

1) representative

2) non-representative, where patients who present for screening are mostly high-risk

3) non-representative, where patients who present for screening are mostly low risk

These scenarios are explored below.

6.2.1.1 The case for a representative sample of the population presenting for densitometry

If the people presenting for densitometry had a similar statistical distribution to the general population (that is, they are a representative sample), then the NNS estimates for a given time period, age, gender and treatment group would be similar to those in Chapter 5. This would be essentially the same as starting with a smaller screened population than that used in our simulations (N=1000).

6.2.1.2 The case for non-random screening where more high risk than low risk patients present for densitometry

More high-risk patients may present for densitometry because they are motivated to attend screening because they know, or they perceive that they have risk factors that may predispose them to developing low BMD. These may include being a postmenopausal woman, or having used high dose corticosteroids on a long-term basis, and so on. There is some literature evidence for this – with one investigation reporting a high prevalence of low BMD in densitometry of self-referred women, with an estimated 60% of women having reduced BMD on screening.[259]

In this situation, NNS estimates for a chosen time period, age, gender, and treatment decision would be decreased, because proportionally more patients of a chosen age and gender who would require treatment than those would not require treatment

attend densitometry. The actual reduction would depend on the difference in fracture risk of the group who present for screening, compared to the underlying population.

6.2.1.3 The case for non-random screening where more low risk than high risk patients present for densitometry

More low risk patients may present for screening DXA because they are less sick or not extremely elderly. Therefore, they are able to leave home and come to where the DXA machine resides, and they are physically able to get up onto the bed underneath the DXA machine and lie flat on their back for 10-15 minutes without any medical consequences. There is some evidence for this, with one study in peri-menopausal women finding that densitometry non-attenders had lower risk of having reduced BMD than attenders. Non-attenders were more likely to be significantly heavier (with high body weight likely to decrease the risk of having low BMD). Other differences between the groups were confounded by social class (sedentary lifestyle) and body weight (lower HRT use).[260] However, the number of non-attenders was small (N=6), and therefore more research is required to ensure this is not a spurious result.

In this situation, the NNS estimates for a chosen time period, age, gender, and treatment decision would be increased over the modelled estimates listed in Chapter 5. This is because more patients would need to be screened to identify the patients to be treated for a chosen time period, age, gender, and treatment decision. The NNT would not change for a chosen time period, age, gender, and treatment decision because the effect of treatment would be the same regardless of how many patients were treated.

Therefore, the strongest evidence suggests that less than 100% of people will present for screening, and that the people who present will have higher risk of low BMD than if those who presented for screening were a random sample of the population as a whole.

6.2.2 Assumption of RCT level of compliance with treatment

Non-compliance with treatment regimens is defined as patients who do not take the medications they have been prescribed in the "correct" manner. The level of compliance assumed by the model is equal to that found in the RCT's on which the estimate of the effect of treatment is based (SeeTable 62). These RCT's are all intent to treat analyses.[243,244,245,145,246,109]

The level of compliance with treatment found in RCT's could be considered to be the "gold standard" level. Achieving higher levels of compliance in regular clinical practice than those found in RCT's is unlikely, because patients who take part in RCT's are likely to be different to regular patients.[147] For example, they may have less co-morbidities and be more motivated to take their tablets as directed than would otherwise have been expected. Non-compliance affects treatment efficacy by reducing the benefit of treatment over placebo.

6.2.2.1 Will patients at medium risk or high risk of developing osteoporotic fractures be more likely to comply with alendronate treatment?

Patients at high risk of developing osteoporotic fractures (eg Z<-2) may be more likely to take their medication at levels similar to the compliance rates found in RCT's than those at medium risk (eg Z-score between –1 and -2). This may be because they are more motivated to receive treatment because they realise they are at high risk for their age of experiencing a fracture. However, the patients at very high risk of sustaining osteoporotic fractures (Z<-2) may be less likely to take prescribed alendronate medication because they may be unable to tolerate or take alendronate medication as directed, not necessarily because they are unmotivated to improve their BMD. Alternatively, they may have gastro-oesophageal co-morbidities, or are bedridden and unable to sit upright for half an hour after taking the tablets. Either scenario, or a combination of both, is possible. However, at the current time there is no evidence to suggest which scenarios may be more accurate.

6.2.2.2 Why treatment compliance is difficult to estimate

While all forms of non-compliance reduce treatment efficacy and therefore increase NNT and NNS, the way non-compliance is defined and the point at which it occurs has implications for cost-effectiveness analyses. For example, patients who undergo screening densitometry, and are identified as having low BMD but who never seek treatment may incur fewer costs than patients whom are prescribed anti-osteoporotic medications but never consume the tablets. The proportion of patients who would not comply at individual stages of the screening and treatment program would need to be estimated – an extremely difficult exercise - and therefore attempts at measuring compliance as part of this modelling exercise have not been attempted.

6.2.3 Why do patients exit the model when they are institutionalised?

There are complex issues and uncertainties around the fracture risk of institutionalised patients, as the change to their fracture risk after institutionalisation is difficult to accurately estimate.

Institutionalised patients may have a higher risk of hip fracture than non-institutionalised patients, as they may be quite elderly, and have additional risk factors for falls, such as reduced muscle strength, Parkinson's disease, poor vision, physical inactivity, psychotropic medications, or medications which may induce postural hypotension.[185]

If patients are suffering mental impairment (such as through dementia), they may have difficulty following instructions for taking alendronate. For example, they may not remember to sit upright after taking the tablets, and go back to bed instead. This would place these people at increased risk of developing serious adverse events relating to alendronate ingestion, such as oesophageal ulceration.[261] Institutionalised patients are a heterogenous group, to which the above considerations apply to a greater or lesser extent. The change in individual or overall fracture risk maybe extremely difficult to estimate, and may be independent of BMD change. Therefore, institutionalised patients have been "dropped out" of the model after their institutionalisation, in a similar manner to patients who have died, because of the difficulties in making accurate estimates of changes to their fracture risk.

6.2.4 Why does the prevalence of having BMD within a particular treatment decision change with age in the COPD population?

The difference between the mean BMD of the COPD and the general populations is always 5%. This is an assumption of the model. However, as the mean BMD of the general population decreases with advancing age, the difference between the general population and the COPD population BMD decreases. Therefore, the lower the mean BMD of the general population becomes (in the oldest age groups), the closer the prevalence of a particular *Z*-score in the COPD population becomes to that of the general population.

The prevalence of a particular treatment decision (such as $Z<-1.0$) in the COPD groups is different between men and women because men and women have a different standard deviation (0.13 g/cm^2 for men and 0.12 g/cm^2 for women).

6.2.5 Robustness of NNS and NNT estimates for 75 year olds after treating with alendronate for ten years

At the age group who begin treatment at age 75 and continue treatment until age 84 (unless exiting the model after experiencing hip fracture, death or institutionalisation), the rates of hip fracture and mortality and institutionalisation are high - both in general and as a result of a hip fracture. With such a large percentage of patients exiting the treatment group due to death, or institutionalisation per annum, especially in the COPD groups, the number of people in the treated group dwindles markedly over ten years - see Table 68 on page 156. We know little about the interaction of all the factors involved at such an advanced age and even less about what may occur in subgroups such as patients with COPD. Therefore, we can not be confident about how the independent contributions of mortality and institutionalisation may change the overall pattern of what happens with the prevention of hip fractures in this age group. Therefore NNS and NNT estimates after alendronate treatment for 10 years in men and women beginning treatment at age 75 has not been tabulated in this thesis. However, the estimates in the same groups after treatment for one year are sufficiently low that policy decisions on whether to screen and treat different subgroups of either the general population or the COPD population with alendronate could be made with the data on one year of treatment only - see Table 69 on page 161. Therefore, estimating NNS and NNT for alendronate treatment after ten years would not be necessary.

6.2.6 How much difference does the Markov simulation (including mortality and institutionalisation) really make on estimates of NNS and NNT?

As discussed earlier, the Markov simulation takes into account patients exiting from the model in a variety of ways (death, institutionalisation) when calculating the outcomes for the following year. Subsequent iterations of the Markov model provide simulated results after a number of years have passed.

By adding the hip fractures prevented for each year when starting treatment at age 55, 65 or 75, and treating patients with BMD at or below the chosen threshold for treatment for 10 years, an estimate of "cumulative hip fractures prevented" is created. This does not take into account deaths or institutionalisations. Comparing this with the estimates of NNS and NNT and hip fractures prevented after ten years of alendronate treatment produced by the Markov model illustrates the difference made by taking mortality and institutionalisations into account (See Table 69). The

ratios of the NNS and NNT estimates developed using the hip fractures prevented from the cumulative model to the hip fractures prevented developed from the Markov model for ten years of alendronate treatment was 0.69 in 55 year olds, and 0.61-0.64 in 65 year old males and females in the general population (regardless of treatment decision). This means that 44-62% increases in NNS and NNT estimates are seen when mortality and institutionalisation are taken into account. The ratio between these parameters in the COPD population are smaller again – with 0.65 – 0.68 in men and women with COPD commencing treatment at age 55, and 0.53 – 0.55 in men and women with COPD commencing treatment at age 65. Therefore, a 47-92% increase in number of people needing to be screened and treated to prevent hip fractures is seen in the COPD population when deaths and institutionalisations are considered. Therefore, estimates of NNS and NNT developed from short term RCT studies may underestimate the true NNS and NNT required to prevent hip fractures.

This has significant implications for screening and treatment programs, and suggests that the NNS and NNT estimates obtained for periods longer than one year need to take into account patients who no longer take treatment (due to death or institutionalisation). The scope of screening programs needs to be increased accordingly, by a factor of 44-92% depending on the age of the patients and whether or not they have COPD.

Conclusion

The model assumption of 100% compliance with screening is unlikely in practice. The most likely alternative scenario is that a higher-risk group than the underlying population would present for screening, which would reduce NNS estimates.

There is insufficient evidence to suggest whether or not patients in the general population would have different levels of compliance to the patients in randomised controlled trials.

The hip fracture rates of institutionalised and extremely elderly patients such as 75 year olds treated for ten years with daily alendronate are surrounded by much uncertainly, and are therefore difficult to accurately assess.

NNS and NNT estimates (after ten years of daily alendronate treatment) may underestimate true hip fracture rates by 50-90% if deaths and institutionalisations are not taken into account.

6.3 Discussion of modelled results

6.3.1 What affects the modelled estimates of NNT?

6.3.1.1 Levels of absolute fracture risk

The most important determinant of NNT is the level of absolute fracture risk. The statistic NNT is the reciprocal of absolute risk reduction (1/ARR)– the reduction in absolute risk conferred in patients receiving the intervention compared to patients receiving the placebo. Therefore, NNT will vary in populations with different underlying risk of the event (in this case, hip fractures) (See subject inclusion criteria in Table 62).

Age and (initial) BMD are the strongest known risk factors for hip fracture and are, in part, independent. Therefore, absolute values for BMD have different significance at different ages.[262] Advancing age is associated with decreased absolute BMD,[10 11] but may also be associated with aging-related physiological changes eg poor balance, poor health or co-morbidities.

6.3.1.2 Other factors contributing to changes in absolute risk

Certain subgroups of the general population have a higher risk of hip fracture. Theses include patients with previous vertebral fractures (subgroup with low BMD in whom fractures have already occurred), and patients with significant co-morbidities, such as COPD.

6.3.1.3 Non-linear effect of alendronate treatment

Data on long term (7-year) treatment in post-menopausal women shows that alendronate increases hip BMD for 3-5 years, and then prevents bone loss for 2 years.[240] Therefore, the duration for which patients are treated will affect absolute risk. This is because response to alendronate treatment is not linear, with patients treated for longer periods of time sustaining lesser increases in BMD (or BMD may remain stable) over the last 1-2 years of 7 years of alendronate treatment than they do in the first 1-2 years. This additive effect has not been included in this model: it is not currently known if this effect continues indefinitely, and there is no data on the effect of alendronate treatment for periods of longer than 7 years.

Treatment effect has been assumed to be linear for the results presented in this thesis. All factors that influence NNT will ultimately influence NNS because NNS is algebraically linked to NNT.

6.3.1.4 Comparison between NNT estimates in the general population and patients with COPD

Despite there being a larger number of people treated for a given age, duration of treatment and treatment decision, there are also a larger number of hip fractures prevented in the COPD group than the general population, because the COPD population has a higher underlying rate of hip fracture. However, the ratio between the number treated and the number of hip fractures prevented in the COPD and the general populations are similar, and thus there are equivalent differences in absolute risk between the treated and non-treated groups ("control" and "intervention" groups) in the COPD and general populations.

This also illustrates that the effect of treatment is the same in both the COPD and the general populations - which was an assumption of the model in any case.

6.3.2 What affects the modelled estimates of NNS?

While NNT estimates are similar for a given treatment decision and gender between both the general population and the COPD population (the model assumes that the effect of treatment is the same in both groups because the fracture rates are the same), the NNS estimates are consistently lower in the COPD group. There are two explanations for this. One can be explained using the "literature" version of the NNS formulae (NNS=NNT/prevalence of disease). The prevalence of having a BMD within *Z*-score groups at the lower end of the normal distribution is higher in the COPD groups because the COPD distribution is shifted down 10% compared to the general population (see prevalence figures for each *Z*-score group in Table 68).

The second explanation is best illustrated using the "model" version of the NNS formulae (NNS = number screened/hip fractures prevented). The number of people screened in the general population and the COPD population is the same (N=1000), but there are more hip fractures prevented in the COPD group because the hip fracture rate is higher. Therefore, screening patients with COPD at an earlier age than people in the general population may be able to be justified because the NNS is lower.

6.3.3 Where are the people having hip fractures in reference to the population?

The lower ends of the normal distribution are over-represented in terms of hip fracture risk, and, as expected, the lowest standard deviation groups have the highest rates of hip fractures for their relative size. For example the *Z*<-2 group in the

general population comprise only 2% of the general population, but 15.8% of the hip fractures, compared to the Z<-1.5 group which has 2.6x as many people (6.7% prevalence) by only 1.9x the fractures.

6.4 How do we assess whether NNS and NNT estimates are reasonable?

NNS and NNT estimates are best used as a component of cost-effectiveness analyses, such as cost per quality adjusted life years gained ($/QALY's), or cost per life years gained ($/LYG) rather than estimates unto themselves. "High" estimates of NNS and NNT may still be cost effective depending on the cost of the intervention and the direct and indirect savings of adverse events prevented. Comparisons can be made to estimates of NNS and NNT for other interventions for chosen time periods, populations and treatment decisions to assess relative efficacies of the interventions.

6.4.1 Literature estimates of NNS and NNT from screening and treatment studies

Literature estimates of NNS and NNT from screening and treatment studies investigating the prevention of deaths from cancer and strokes are listed in Table 70 and Table 71. Considerations of these NNS and NNT estimates illustrate a number of useful points.

Consideration of the studies on anti-hypertensive drugs listed in Table 71 provides additional data to support the importance of using models to simulate NNS and NNT estimates. There are similar issues in hypertension as there are in osteoporosis regarding the effect of advancing age on hypertension, the choice of blood pressure reading to use as a treatment decision, and the mode of measurement used to determine blood pressure. In addition, clinical trials may not be representative of the underlying population.

It is fundamental that NNS and NNT estimates be considered to be specific for a particular population with a specified underlying risk of the adverse event, for treatment with a particular agent for a specified period of time. Pooling numbers needed to treat may not be reliable, as the background level of risk varies between trials in a non-random fashion, and will confound the treatment effect.[263] The use of different entry criteria, such as age, or disease criteria like blood pressure or BMD, or even the use of different equipment to measure different criteria - will also change the prevalence of the group treated in the general population, affecting the number

needed to screen. However, pooled NNS and NNT estimates are still created by some authors, despite these problems[242] – See Table 70 and Table 71.

Despite these issues, when the NNS and NNT estimates generated by our model (Table 72) are compared with the NNS and NNT estimates tabulated in Table 71, the comparisons are favourable. The NNT estimates for treating 65 year old women in either the general population or the COPD population for 10 years, or treating 75 year old women (in either population) for 1 year are well within the ranges of NNT for preventing deaths using anti-hypertensive and anti-dyslipidemic drugs for 4-9 years. The ranges of absolute and relative risks are similar between the treatments preventing death from cardiovascular disease. The NNS estimates are much higher for the prevention of hip fractures than prevention of deaths form cardiovascular disease (the prevalence of having Z<-1.5 is much lower than the prevalence of hypertension or dyslipidemia). However, the NNS for preventing hip fractures with alendronate listed in Table 72 are either comparable or much lower than the NNS estimates for preventing cancer-specific mortality from breast or colorectal cancer from screening trials over 8-9 years.

Therefore, the NNS and NNT estimates developed from our modelling analysis are comparable to NNS and NNT estimates available for treatment of other conditions using various interventions. In particular, the estimates of NNT and NNS for screening and treating: 75 year old women for 1 year (either in the general or COPD population), 65 year old women with COPD for 1 and 10 years, and 65 year old women in the general population for 10 years appear particularly promising. However, as stated earlier, NNS and NNT estimates need to be considered within the context of cost-effectiveness analyses to decide if the groups listed above would be cost-effective to screen and treat.

Table 70 – NNS and NNT to prevent 1 death for screening programs to prevent cancer of the breast and colon (from Rembold *et al.* 1998[242])

	Trial duration (years)	Number of		Risk reduction (%)		NNS
		Trials	Patients	Relative	Absolute	
Cancer specific mortality						
Screening haemoccult[264]	8.5	3	13,073	23	0.12	808
Screening mammography[265-267]	8.5	7	372,612	19	0.05	1,887
Age 60-69	9	1	71,444	31	0.14	695
Age 50-59	8	2	149,849	23	0.06	7,532
Age 40-49	8	2	136,763	13	0.02	4,576
Total mortality						
Screening haemoccult[264]	3.1	1	21,757	1	0.02	4,894
Screening mammography[265-267]	7.2	1	89,835	-1.4	0	-7,660§

§ Negative NNS indicates that mortality was higher in the screened population.
NB These are screening trials where the outcome of interest was deaths, rather than a surrogate endpoint. Therefore, no NNT estimates have been listed. See Chapter 5.2.

Table 71 – NNS and NNT to prevent one death with cardiovascular agents in patients with no atherosclerotic cardiovascular disease (from Rembold *et al.* 1998[242])

	Trial duration (yrs)	Number of		Risk reduction (%)				
		Trials	Patients	Relative	Absolute	NNS	Prevalence (%)	NNT
Anti-hypertensive drugs								
Diuretics – Blood pressure decrease of 10.0[268-271]	5.6	4	3,141	18	2.2	2	18	43
Diuretics – Blood pressure decrease of 5.7[269-278]	5.4	11	48,013	8	0.4	12	18	213
Beta blockers – Blood pressure Decrease of 6[272]	5.2	3	22,729	6	0.3	22	15	332
Anti-dyslipidaemic drugs								
Pravastatin[279,280]	4.3	2	7,657	22	0.7	5	26	126
Diet[281]	9	1	1,232	31	1.1	3	26	85
Resin[282,283]	5.4	2	6,084	13	0.4	8	26	203
Aspirin[284,285]	5.2	2	27,212	8	0.2	13	26	340

Table 72 - NNS and NNT to prevent one fracture with alendronate treatment for 1 - 10 years in women in the general population and with COPD

	"Trial" duration (yrs)	Number of		Risk reduction (%)				
		Trials	Patients	Relative	Absolute	NNS	Prevalence (%)	NNT
Hip fractures								
75 years (COPD)	1	n/a	20	24	1.2	422	20	82
75 years (general population)	1	n/a	67	26	1.1	1,301	7	87
65 years (COPD)	1	n/a	21	26	0.3	1,840	7	380
65 years (COPD)	10	n/a	21	13	2.9	165	7	34
65 years (general population)	1	n/a	67	27	0.2	6,105	7	408
65 years (general population)	10	n/a	67	8	3.4	438	7	29
Black, 1996.[243]	3	1	2,027	51	1.1	979	9.18	90
Vertebral fractures								
Cummings, 1998[244]	4	1	4,432	21	0.2	1,083	41	447

† Estimates are for treating women (either in the general population or the COPD population) with Z<-1.5, and beginning treatment with daily alendronate (10 mg) at age indicated. The data on osteoporosis trials (except Black *et al.* 1996[243] and Cummings *et al.* 1998[244]) are from the modelled estimates of NNS and NNT discussed in this thesis.

Conclusion

NNS and NNT estimates generated as part of this project are comparable to other NNS and NNT estimates available in the literature. However, before it is decided whether screening and treating any subgroups of the COPD or general populations is worthwhile, NNS and NNT estimates need to be considered in the context of other cost-effectiveness analyses.

Chapter 6 conclusion

- 100% compliance with screening is unlikely to occur in practice. The people who present for screening are more likely to be at higher risk of having low BMD than those who do not attend. This may reduce NNS estimates
- There is no evidence to suggest whether or not patients in the general population would have different levels of compliance with treatments to the patients who participated in randomised controlled trials of daily alendronate.
- It is difficult to accurately estimate the hip fracture rates of people who are institutionalised or extremely elderly patients, such as 75 year olds treated for ten years

- NNS and NNT estimates after ten years of daily alendronate treatment may underestimate true hip fracture rates by 50-90% if deaths and institutionalisations which take place over that ten year period are not taken into account.
- The number of people who need to be treated (NNT) to prevent one hip fracture is approximately equal for people in the general population, and people with COPD of the same gender, BMD who are treated for the same length of time with daily alendronate.
- NNS estimates are consistently lower in the COPD group (compared to people in the general population) for groups of the same gender, BMD and period of daily alendronate treatment. This is because the prevalence of low BMD and the rates of hip fracture are higher for any particular *Z*-score group in the COPD population. Therefore, treating patients with COPD may be justified at a younger age than for people in the general population.
- NNS and NNT estimates generated as part of this project are comparable to other NNS and NNT estimates available in the literature. However, these estimates need to be considered within the context of a cost-effectiveness analysis before deciding whether screening and treating any subgroups of the COPD or general populations is worthwhile.

Chapter 7 – Combining the results of a risk factor analysis with results from number needed to screen and number needed to treat modelling

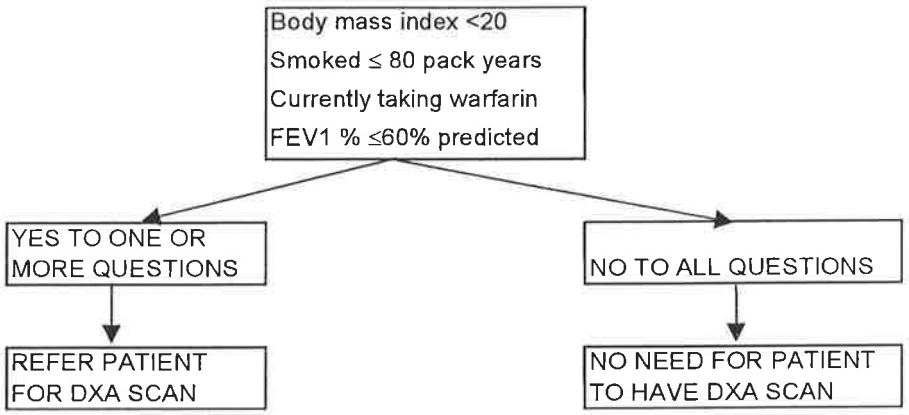
7.1 Development of an algorithm for identifying COPD patients requiring bone densitometry

Earlier in this thesis a risk factor model which can be used to identify 35% of patients with asthma or airways disease who do NOT require bone densitometry has been described (See Table 44 in Chapter 4.6.7).

The results from the risk factor model could be developed into a screening algorithm such as Figure 18.

WHICH OF YOUR RESPIRATORY PATIENTS SHOULD YOU REFER FOR BONE DENSITY TESTING?

People who have ASTHMA, EMPHYSEMA, CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD), or CHRONIC BRONCHITIS and who answer YES to any of the following are recommended to have a bone density test using dual x-ray absorptiometry (DXA)[§]



IF MY PATIENT HAS LOW BONE DENSITY, HOW MUCH DIFFERENCE WILL TREATMENT MAKE?

Daily alendronate (10mg/day) increases bone density of the femoral neck by 3.0 – 6.2%; and lumbar spine by 6.2 – 8.8% over 3-4 years in post-menopausal women.[244,243,245,145] Treatment reduces the relative risk of fractures of the hip and spine by 21-51% and 45-55% in relative terms (relative risk reduction) and 0.22-1.1% and 1.6-2.7% in absolute terms (absolute risk reduction).[244,243,145]

HOW MUCH WILL THE TEST COST?

The Medicare scheduled fee is $68.85 for a DXA of hip and spine.[13]

HOW CAN MY PATIENT OBTAIN A FREE BONE DENSITY TEST?

Patients with certain medical conditions can obtain a free DXA scan eg glucocorticosteroid use. Consult the current edition of the Medicare Benefits Schedule Book for more details.[13]

Patients who have bone density in the lowest 6.5% for their age and gender (*Z*-score $Z<-1.5$) are eligible for free DXA tests every 2 years after their initial DXA scan.[13]

Figure 18 – Information for physicians to aid in identifying patients to send for bone densitometry

[§] Developed in a study population aged 45-79 years with risk factors for osteoporosis. Exclusion criteria include contraindications for alendronate treatment.

7.2 Application of reduction in patients requiring screening to number needed to treat

There are two major components to this thesis:

a) a method for determining the number needed to screen and number needed to treat for preventing hip fractures with daily alendronate has been described in chapter 5.13, with results in Table 68 and Table 69 on pages 159 and 161.

b) the results of the risk factor model for identifying people with respiratory disease who are at increased risk of having low age- and gender-matched BMD as described in Chapter 4 (which begins on page 98), and in Figure 18 on page 179.

Combining these two concepts enables the estimation of the scale of a disease-screening program in men and women with asthma and airways disease, which identifies high-risk persons who would benefit from densitometry.

The pre-screening tool recommends that 65% of patients receive densitometry, and that 35% are excluded from densitometry. Those who are recommended for densitometry will include most of the people who have low BMD, and are therefore at higher risk of sustaining a hip fracture, but does not include all of them (false negative rate of 14%). Therefore, the number of hip fractures prevented has been adjusted because some patients (14%) who have low BMD (Z<-1.5) will have been missed (sensitivity =86%). Therefore, the formulae listed in Chapter 5.12 on page 158 needs to be modified from the following formulae:

$$\text{NNS} = \frac{\text{number of people screened}}{\text{Number of hip fractures prevented}}$$

$$= \frac{\text{number of people screened}}{\text{number of hip fractures in "control" group} - \text{number of hip fractures in "intervention" group}}$$

to:

$$\text{NNS} = \frac{\text{number of people screened in model (=1000)} * 0.65}{\text{number of hip fractures in the "control" group} - ((\text{number of hip fractures in the control group} * 0.14) + (\text{number of hip fractures in the "intervention" group} * 0.86))}$$

Therefore, the new number of hip fractures for the "intervention" group will consist of 86% of people who receive treatment - and therefore have the reduced hip fracture rate of treated patients); and 14% of people assigned to the "intervention" group who will not receive treatment - and therefore will have the hip fracture rate of untreated or "control" patients.

Correspondingly, the NNT is changed from this:

$$NNT = \frac{1}{\text{"event rate" in "control" group} - \text{"event rate" in "intervention" group}}$$

to this:

$$NNT = \frac{1}{\text{"event rate" in "control" group} - \text{((event rate in the "control group"*0.14) + (event rate in the "intervention" group* 0.86))}}$$

Therefore, the new event rate for the "intervention" group will consist of 86% of people receiving treatment (and therefore have the reduced hip fracture rate of treated patients) and 14% of people assigned to the "intervention" group who will not receive treatment and therefore will have the hip fracture rate of untreated or "control" patients.

The *rates* of the events have been used to calculate NNT, whereas the *number* of events have been used in the NNS calculations. This is because I considered that in each case, these were the simplest formulaes to use – there are alternate algebraic expressions for these formulae (See Chapters 5.11 and 5.12).

The results of using the adjusted NNS and NNT formulae to derive NNS and NNT estimates are listed in Table 74, alongside the original estimates derived from the distribution model.

Table 73 – NNS and NNT for preventing hip fractures with treatment with daily alendronate (10mg) for one year with the use of the pre-screening tool

FEMALES		Results from distribution model		Using pre-screening tool	
Start treatment at age	Treatment decision (*Z*-score)	NNS	NNT	NNS	NNT
55	<-1	5,150	2,035	3,892	2,367
	<-1.5	6,758	1,499	5,108	1,744
	<-2	10,279	1,057	7,769	1,229
65	<-1	1,383	519	1,045	603
	<-1.5	1,840	380	1,391	442
	<-2	2,848	267	2,152	310
75	<-1	313	112	237	131
	<-1.5	422	82	319	95
	<-2	662	57	500	67
MALES					
55	<-1	12,675	5,015	9,580	5,831
	<-1.5	16,627	3,695	12,567	4,297
	<-2	25,281	2,604	19,108	3,028
65	<-1	3,848	1,469	2,908	1,708
	<-1.5	5,096	1,079	3,852	1,254
	<-2	7,841	758	5,926	881
75	<-1	864	321	653	374
	<-1.5	1,152	235	871	274
	<-2	1,787	165	1,351	192

NNS estimates are reduced by 25% in each *Z*-score group, age and gender when the pre-screening tool is used. Explanations include:

a) fewer people are screened (because 35% are eliminated from screening)

b) fewer hip fractures are prevented (because 14% of those who would receive treatment under "modelled" conditions would not receive treatment when the pre-screening questionnaire is used prior to densitometry)

However, the ratio between a) and b) above results in the screening of a higher-risk group than if the entire group had received densitometry.

NNT estimates are a little higher in each *Z*-score group, (16%) age and gender when the pre-screening tool is used. Explanations include:

a) fewer hip fractures prevented because there is a reduction in the difference in absolute risk of hip fractures between "control" and "intervention" groups

b) fewer people are treated

7.3 Conclusion

This chapter presents results for the NNS and NNT for preventing hip fractures with daily alendronate in men and women with COPD aged 55-75 and with BMD of Z<-1.0, Z<-1.5, and Z<-2.0 after the use of the pre-screening tool discussed in Chapter 4 (which has sensitivity of 86% and specificity of 41%). This is done by taking account of the lesser number of patients screened and the change in the hip fracture rate or number of hip fractures than under ideal or ("modelled") conditions.

The use of the pre-screening tool prior to densitometry captures a higher-risk population than if everyone was screened, and everyone with low BMD was treated. However, since 14% of patients who would otherwise fulfil the requirements of treatment (because they have low enough BMD) are not treated (false negatives), the effectiveness of treatment is reduced by just over 14% (16%).

7.4 General conclusion

The cost-effectiveness of using the pre-screening tool prior to DXA depends on the cost of all components – densitometry, alendronate treatment, and costs of missed cases of low bone density such as nursing home admissions, hospitalisation and so on. The cost of missed cases of low BMD may outweigh the cost of a larger screening program in which all people with COPD aged 55 –75 receive densitometry.

An alternative to the disadvantages of using the pre-screening model discussed above is to recommend ALL patients aged 55-75 with COPD receive densitometry, but the final decision on which model to use would ultimately be decided by cost-effectiveness analyses, taking into account the cost of screening, fractures sustained and savings encountered by preventing fractures.

Chapter 8 – Thesis conclusions

Chapter 2.1 – Does low bone density cause sufficient mortality and morbidity to warrant routine screening?

Large numbers of Australians sustain fractures (particularly hip fractures) and the associated poor outcomes have significant public health implications. This magnitude of the problem will increase dramatically over time as Australia's population ages, and there are more people in the age groups with high fracture incidence. People with chronic airways limitations such as asthma, emphysema and COPD have high levels of actual bone fracture, low BMD, and associated high risk of developing osteoporotic fractures. Consequently, the morbidity and mortality associated with osteoporotic fractures for this group is particularly large. The projected number of fractures in the next 30-50 years is sufficiently large to consider a case for screening for low BMD in patients with moderate to severe airways disease, with a view to lowering fracture rates in this group of people with treatments for low bone density.

Risk factors for low BMD in patients with asthma or COPD include both risk factors applicable to the wider community (such as activity, steroids, catabolic status advancing age, low body weight) and also risk factors specific to respiratory disease (such as poor lung function). Both general population and disease-specific risk factors ought to be considered when designing a screening strategy to identify patients at higher risk of developing low bone density. In people with more severe disease, the negative effect of taking corticosteroids, high alcohol and cigarette consumption may overshadow small effects of other factors eg low calcium intake on bone density.

Chapter 2.2 – Is early treatment for low BMD during the pre-fracture phase effective in preventing or reducing morbidity and mortality?

There are a number of treatments available for preventing osteoporotic fractures that have been trialed in patients with respiratory disease, and people requiring daily oral corticosteroids. The most effective treatments are bisphosphonates (especially risedronate and alendronate). Most of the treatments studied in people taking daily oral corticosteroids (including people with respiratory disease) are available in Australia, but most treatments available are very expensive for the majority of

patients who are not able to meet the PBS indications to receive the treatment at a subsidised price.

Chapter 2.3 – Is a screening test available that is reasonably inexpensive, safe and acceptable to patients?

DXA tests are cheap, safe, widely available, and the most dependable technique currently available.

Chapter 2.4 – Does the screening test have adequate predictive value?

Numerous guidelines have been drafted to identify patients at high risk of osteoporotic fractures. However, their recommendations are inconsistent and not implemented in regular clinical practice.

Evidence-based, systematic approaches to identifying high-risk subgroups for low BMD prior to densitometry have been investigated. Most non-SCORE questionnaire did not reach the "gold standard" of 90% sensitivity, but SCORE validations did in most populations studied. These screening tools may prove to be a cost-effective addition to densitometry by reducing the number of patients requiring densitometry by 10-33%.

Chapter 3 – Methodology of the development of a risk factor analysis to develop a screening tool to identify patients with respiratory disease who are at increased risk of low bone density.

People with moderate to severe asthma, emphysema, COPD or chronic bronchitis who had attended respiratory outpatients or had been hospitalised for their airways disease at The Queen Elizabeth Hospital, the Lyell McEwin Health Service, or the Royal Adelaide Hospital over 1999-2002 were targeted for the study. In addition, patients were sourced from a number of general practices in the Adelaide Western Division of General Practice as well as a number of other sources. Patients who scored more than 5 points on our pre-screening questionnaire and satisfied other inclusion and exclusion criteria were invited for densitometry, and completed a more detailed questionnaire on their health (screening questionnaire). This data was used to test Hypothesis 1: that patients with "low" ($Z<-1.5$) or "not low" ($Z>-1.5$) age- and gender-matched BMD at either the neck of femur, total femur or lumbar spine differed significantly for one or more risk factors for low BMD using a χ^2 test for categorical variables, or logistic regression for continuous variables.

Chapter 4 – Results of a risk factor analysis to develop a screening tool to identify patients with respiratory disease who are at increased risk of low bone density.

Our sample was middle aged, with more men than women. Both men and women were overweight and sedentary compared to reference populations. Men and women had different patterns of risk factors, and the men had poorer health and lower age- and gender-matched BMD than the women. Individual risk factors that were associated with low BMD (with genders pooled) ($p<0.25$) were included in the multivariate analysis. At a p value of entry of 0.1, the multiple logistic regression "model" comprised three factors – having a body mass index <20, smoking >80 pack years of cigarettes, FEV_1 ≤60% predicted, and current use of warfarin. The combination of these four risk factors corresponded to a sensitivity of 86% and specificity of 41% and correctly classified 50% of patients. This was chosen in preference to an alternative model comprising 96% sensitivity and 21% specificity, which had a higher sensitivity but a poorer overall mix of sensitivity and specificity, correctly classifying only 36% of patients. The chosen model had a positive predictive value of 27%, and a negative predictive value of 92%, and had an area under the ROC curve (AUC) of 0.7. People who did not have any of the four risk factors in the multivariate logistic regression (comprising 65% of our sample) who had a risk of having $Z<-1.5$ of 13% or less would *not* be recommended for densitometry. The use of pre-screening questionnaires has the potential to reduce the cost of screening programs by ~20% by identifying subgroups who would not benefit from densitometry.

Chapter 5 – Methods and results for modelled estimates of number needed to screen and number needed to treat to prevent hip fractures over one and ten years with daily alendronate

Number needed to screen (NNS) is a measure of the number of people with defined characteristics who need to be screened (and then treated) for a disease to prevent one death or adverse event for a particular period of time. Number needed to treat (NNT) is number of people who need to be treated with a certain agent for a particular period of time to prevent one death or adverse event. Providing screening is useful, NNS (and NNT) provide a tangible guideline for busy clinicians to conceptualise the scale of disease screening and treatment programs. NNS and NNT estimates based on modelled populations provide information for today that is relevant to the underlying population. Literature equations were used to estimate hip

fracture rates, the effect of COPD and treatment with daily alendronate on BMD in the short term. The rate of hip fractures in the longer term (and also the effect of fractures, mortality and institutionalisation on hip fracture rates and hence NNS and NNT) was simulated after ten years using a Markov simulation.

NNS estimates are lowest in the groups with highest BMD eg Z<-1.0 where disease prevalence and hip fracture rates are lowest. NNT estimates are lowest in the groups with lowest BMD where the disease prevalence and hip fracture rates are highest. Approximately 6100 65 year old women in the general population with BMD of Z<-1.5 need to be screened and 408 need to be treated to prevent one hip fracture with daily alendronate treatment for one year. For ten years of daily alendronate treatment ~430 of these women would need to be screened and ~39 treated to prevent one hip fracture. Approximately ~1840 65 year old women in the COPD population with BMD of Z<-1.5 need to be screened and 380 need to be treated to prevent one hip fracture with daily alendronate treatment for one year. For ten years of daily alendronate treatment ~165 of these women would need to be screened and ~34 treated to prevent one hip fracture.

Chapter 6 – Discussion of modelled estimates of number needed to screen and number needed to treat to prevent hip fractures over one and ten years with daily alendronate

Chapter 6.1 – Challenges to model inputs

Hip fractures were chosen because this fracture type is easily identifiable with few fractures evading detection, and results in high rates of mortality and morbidity. We chose to use Commonwealth data because no local population-based data is available, and national hospital statistics can be generalised to the overall Australian community.

Chapter 6.2 – Challenges to model assumptions

The model assumption of 100% compliance with screening is unlikely in practice. The most likely alternative scenario is that a higher-risk group than the underlying population would present for screening, which would reduce NNS estimates.

There is insufficient evidence to suggest whether or not patients in the general population would have different levels of compliance to the patients in randomised controlled trials.

The hip fracture rates of institutionalised and extremely elderly patients such as 75 year olds treated for ten years with daily alendronate are surrounded by much uncertainly, and are therefore difficult to accurately assess.

NNS and NNT estimates (after ten years of daily alendronate treatment) may underestimate true hip fracture rates by 50-90% if deaths and institutionalisations are not taken into account.

Chapter 6.3 – Discussion of modelled results

The number of patients needing to be treated (NNT) is approximately equal for patients with COPD and in the normal population for groups of the same gender, BMD and treatment period.

NNS estimates are consistently lower in the COPD groups for people of the same gender, BMD and treatment period as the prevalence and hip fracture rates are higher for a given group in the COPD population.

Chapter 6.4 – How do we assess whether NNS and NNT estimates are reasonable?

NNS and NNT estimates generated as part of this project are comparable to other NNS and NNT estimates available in the literature. However, before it is decided whether screening and treating any subgroups of the COPD or general populations is worthwhile, NNS and NNT estimates need to be considered in the context of other cost-effectiveness analyses.

Chapter 7 - Combining the results of a risk factor analysis with results from number needed to screen and number needed to treat modelling

This chapter presents results for the NNS and NNT for preventing hip fractures with daily alendronate in men and women with COPD aged 55-75 and with BMD of Z<-1.0, Z<-1.5, and Z<-2.0 after the use of the pre-screening tool discussed in Chapter 4 (which has sensitivity of 86% and specificity of 41%). This is done by taking account of the lesser number of patients screened and the change in the hip fracture rate or number of hip fractures than under ideal or ("modelled") conditions.

The use of the pre-screening tool prior to densitometry captures a higher-risk population than if everyone was screened, and everyone with low BMD was treated. However, since 14% of patients who would otherwise fulfil the requirements of

treatment (because they have low enough BMD) are not treated (false negatives), the effectiveness of treatment is reduced.

Chapter 7.4 – General conclusion

The cost-effectiveness of using the pre-screening tool prior to DXA depends on the cost of all components – densitometry, alendronate treatment, and costs of missed cases of low bone density such as nursing home admissions, hospitalisation and so on. The cost of missed cases of low BMD may outweigh the cost of a larger screening program in which all people with COPD aged 55 –75 receive densitometry.

An alternative to the disadvantages of using the pre-screening model discussed above is to recommend ALL patients aged 55-75 with COPD receive densitometry, but the final decision on which model to use would ultimately be decided by cost-effectiveness analyses, taking into account the cost of screening, fractures sustained and savings encountered by preventing fractures.

Appendices

Appendix 1 - Summary tables of studies included in Chapter 1 (Table 74, Table 75, Table 76)

Appendix 2 - pre-screening questionnaire

Appendix 3 - Screening questionnaire

Appendix 4 – Bone mineral density reference data (Table 77)

Appendix 5 - Hip fracture incidence (Table 78)

Appendix 6 - Worked examples of calculation of pre-treatment fracture rates

Appendix 7 – Conference abstracts

Table 74 - Summary of study population of risk-factor studies in the general population

Study	Country of origin	Source population	N=	Gender	Menopausal status if female			Age range	Average age	Bone sites measured	DXA?	Exclusion criteria	Analysis/ units
					pre	peri	post						
Bauer, 1993[59]	U.S.A.	White women, from population based listings	9704	F			✓	≥65	71	R, C	✓	Unable to walk unaided, bilateral hip replacement	Correlation
Ribot, 1992[61]	France	Normal white women referred to menopause clinic	1564	F		✓	✓	40-65	54	LS (DPA)	×	No diseases known to affect bone metabolism	Multiple logistic regression
Hansen, 1991[94]	Denmark	Women in placebo arm of RCT 6mo-3yr post menopause	121	F			✓	-	63	LS, NOF, Ward's, Troch	✓	No diseases known to affect bone metabolism	t-test
McKnight, 1995[205]	Ireland	Women from a general practice	358	F	✓	✓	✓	48-52	-	LS	✓		Multiple regression
Slemenda, 1990[66]	U.S.A.	White volunteers in good health	124	F		✓		44-55	50	R (SPA); LS, NOF (DXA)	✓	Not taking medications known to affect bone metabolism	Correlation
Stevenson, 1989[62]	England	White volunteers	284	F	✓		✓	21-68	-	LS, NOF, Ward's, Troch (DPA)	×	-	Correlation
Torgerson, 1995[72]	Scotland	White women, from population based listings	1227	F	✓			45-49	-	LS, NOF, Ward's, Troch	✓	Hysterectomy, using HRT	Multiple linear regression
Ballard, 1998[73]	U.K.	Women aged 70-79 from population based listings	823	F			✓	70-79	-	LS, NOF	✓	Terminal illness, unable to undergo DXA eg obese	Logistic regression
Elliot, 1993[60]	N.Z.	Healthy volunteers	451	F& M	✓	✓	✓	20-83	-	LS, NOF (DPA)	×	-	Multiple linear regression
Nguyen, 1994[74]	Australia	Electoral roll	709 M 1080 F	F& M			✓	>60 years	69	LS, NOF	✓	Osteophytes or scoliosis on BMD scan, nil else	Multiple linear regression

Table 75 - Summary of study population of cross-sectional risk-factor studies in patients with asthma or COPD

Study	Country of origin	Source population	N=	Gender	Menopausal status if female			Age range	Average age	Bone sites measured	DXA?	Exclusion criteria	Analysis/ units
					pre	peri	post						
Wong, 2000[65]	U.K.	Asthmatics taking ICS for >6 months, few OCS, sourced from general practices	196	Both	✓			20-40	32	LS, NOF, Ward's, Troch	✓	OCS course in last 6 months or >2 ever, other disease or medications affecting bone metabolism	Multiple linear regression
Toogood, 1995[81]	Canada	Ambulatory asthmatic outpatients stratified for steroid usage	69	Both	✓		✓	-	60	LS, (DPA & DXA)	✓	-	ANCOVA
Thompson, 1997[70]	U.S.A.	Ambulant women taking low dose OCS & HRT recruited from media advertisements - 12% asthmatics	76	F			✓	-	-	LS, NOF	✓	-	Multiple linear regression
Laatikainen, 1999[64]	Finland	Population-based survey of asthmatics	119	F	✓	✓	✓	47-56	54	LS, NOF			
Iqbal, 1999[71]	U.S.A.	Respiratory outpatients with COPD	171	M				23-90	62	LS, NOF	✓	No medications for bone disease/ osteoporosis except steroids	χ^2

Table 76 – Summary of study population of case-control risk-factor studies in patients with asthma or COPD

Study	Country of origin	Source population	N=	Gender	Menopausal status if female			Age range	Ave age	Bone sites measured	DXA?	Exclusion criteria	Analysis/ units
					pre	peri	post						
Ip, 1994[63]	Hong Kong	Asian asthmatics (hospital clinics); age-, sex-matched controls	30 cases: 30 controls	Both	✓			-	32±9	LS, NOF, Ward's, Troch	✓	Controls - any diseases, medications affecting BMD	Spearman rank correlation
Lau, 1998[88]	Hong Kong	Asian asthmatics (hospital clinics); age-, sex-matched controls	144 cases: 212 control	Both	✓		✓	≥18	-	Total body, LS, hip	✓		t-test, $\chi 2$
Sivri, 2001[69]	Turkey	Asthmatics outpatients using ICS >3 months; age- sex-, menopausal status- BMI-matched controls	32 cases: 26 controls	F	✓		✓		54	LS, NOF, Ward's triangle, trochanter	✓	pregnancy, history of any disease, alcoholism, medications affecting bone metabolism	Correlation (Spearman and Pearson's)

Patient label

GP's details:

This is a study for men and women aged between 45 and 80 years of age with asthma or airways disease

- ✓ The person must have asthma, emphysema, COPD or chronic bronchitis
- ✓ They must not currently be taking alendronate (Fosamax)
- ✓ They must not currently be taking Losec (Omeprazole), Somac (Pantoprazole), or Zoton (Lansoprazole)

If your patients' scores add to five (5) or more in the following list, they are eligible to participate in screening for the Osteoporosis fracture prevention trial in asthma, emphysema and chronic bronchitis which is being conducted on patients from TQEH, LMHS and the Royal Adelaide Hospital at TQEH.

★ A woman aged over 50 years of age? ☐ 2

★ Admitted to hospital at least once for respiratory illness in the last five years? ☐ 2

★ Bone fracture since age 40? ☐ 2

★ Light for height? ☐ 1

Calculation - $\frac{[\text{weight (kg)}]}{[\text{height}^2\ (\text{m})]} \leq 18$ Weight ..... Height .....

★ Spirometry FEV1 < 75% of predicted? (score, % predicted) ..... ☐ 1

FEV1 < 50% of predicted? (score, % predicted) ..... ☐ 2

(FVC (score, % predicted) .....)

★ Physical activity? Limited? (able to walk less than 300m unaided) ☐ 1

Severely limited? (able to walk less than 100m unaided) ☐ 2

★ Used more than 3 courses of oral steroids in the past 2 years? (No. .....) ☐ 2

★ Used high doses of puffer steroids eg ≤1.5 mg/day beclamethasone dipropionate for ≤2 years or equivalent. Record name/dosage: ☐ 1

★ Current or previous smoker of ≤40 pack years? ☐ 1

Duration total .....

Average amount smoked/day .....

➔ *if this score totals to 5 or more then this patient is eligible for the screening phase of the study*

Exclusion criteria

People with moderate/severe renal insufficiency, women with current or planned pregnancies, people with oesophageal stricture, oesophageal achalasia, inability to stand/sit upright for 30 mins, upper gastrointestinal conditions eg dysphagia, gastritis. (Australian Medicines Handbook 1998)

Bone density screening questionnaire

Today's date:

Screening number **Name:**

Telephone number:

Alternative contact:

Age: (DOB must be 1 Jan 1920 – 31 December 1955 in 2000)

Height (cm)

Check General Practitioner address is correct ☐

★ What do the doctors tell you is wrong with your lungs? eg COPD, asthma, emphysema, chronic bronchitis, C.A.L., other

★ Any other illnesses? (especially liver disease, thyroid disease, epilepsy (taking anti-convulsant)

★ List current medications below, include dose

i) vii)

ii) viii)

iii) ix)

iv) x)

v) xi)

vi) xii)

★ Currently taking:

★ Hormone replacement therapy Yes ☐ No ☐

★ Calcium tablets Yes ☐ No ☐

★ Thyroxine (Oroxine) Yes ☐ No ☐

★ Maintenance oral prednisolone Yes ☐ No ☐

★ Anticonvulsants Yes ☐ No ☐ Name:

★ Current use diuretics (fluid tabs) Yes ☐ No ☐ Name:

★ Ever taken any diuretics? Yes ☐ No ☐ Name:

(Thiazide diuretic? Yes ☐ No ☐)

★ Calcitriol (Rocaltrol) Yes ☐ No ☐

★ Theophylline (Theo Dur) Yes ☐ No ☐

★ Heparin/warfarin Yes ☐ No ☐

★ Did your mother ever break any bones after she was 40?

★ Yes ☐ No ☐ Don't know ☐

★ Have you taken any booster courses of steroid tablets over the past 2 yrs?

These are usually known as Prednisolone, Panafcort, or Cortisone Yes ☐ No ☐

Number

Do you smoke or have you smoked? Yes ☐ No ☐

If yes, for how long? years. (Started Stopped)

How many cigarettes per day (on average) did you smoke over this time?

★ Have you reached menopause? Yes ☐ No ☐

★ If yes, how old were you when you reached menopause?

★ Have you broken any bones since you were 40 years old? Yes ☐ No ☐
If yes, where did the fracture(s) take place?

Wrist ☐ Spine ☐ Hip ☐ Ribs ☐ Leg ☐ Foot ☐
Toes ☐ Ankle Other ☐ _____

★ Have you had either of your hips replaced? Yes ☐ No ☐ If yes, which one?

★ How many times have you been admitted to hospital for lung problems in the last 5 years? (include year)

None ☐ 1-2 ☐ 3-5 ☐ 5+ ☐ Year(s) _____

★ I'd like to get an idea of your exercise tolerance. Can you please tell me how far you can walk by yourself in one go?

More than 300m? ☐
Less than 300m? ☐
Less than 100m? ☐

★ <u>Leisure time activity:</u>
I've got some questions I'd like to ask you about the activity that you do during your leisure time. These questions might sound a little silly depending on what you actually do but I'd like you to answer them as asked.

During leisure time do you play sport?
never / seldom / sometimes / often / always
During leisure time do you watch TV?
never / seldom / sometimes / often / always
During leisure time do you walk?
never / seldom / sometimes / often / always
During leisure time do you ride a bike?
never / seldom / sometimes / often / always
During leisure time do you do heavy outside work (eg lawn mowing)
never / seldom / sometimes / often / always
How many minutes did you walk &/ or ride a bike per day to and from work, or shopping?
less than 5 minutes / 5 to 15 / 15 to 30 / 30 to 45 / more than 45 minutes
(12 blocks = 20 mins of brisk walking = 1 mile)

Table 77 – Reference bone mineral density data showing mean and standard deviation for males and females in the reference population (Lunar data[217])

	Females	Males
Age	Mean BMD (g/cm^2)	Mean BMD (g/cm^2)
20 to 29	0.998	1.098
30 to 30	0.973	1.045
40 to 49	0.946	0.984
50 to 59	0.881	0.956
60 to 69	0.818	0.909
70 to 79	0.767	0.876
Standard deviation	0.12	0.13

Table 78 – Number of separations for fracture of femur (ICD-9-CM 820,821 ICD-10-AM S72), sex and age group - 1994/95 to 1998/99 for private and public hospitals, Australia (Source: Australian Institute of Health and Welfare)

Number of separations for fracture of femur(ICD-9-CM 820,821 ICD-10-AM S72), sex and age group – 1994/95 to 1998/99										
	1994/95		1995/96		1996/97		1997/98		1998/99	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
0-4 yr	314	165	350	180	311	156	364	172	332	169
5-9 yr	192	89	201	84	195	90	183	77	195	90
10-14 yr	228	95	251	87	250	78	243	75	266	77
15-19 yr	269	80	280	55	309	55	285	62	306	71
20-24 yr	265	69	274	72	260	59	236	64	249	54
25-29 yr	179	49	171	51	197	55	223	43	188	53
30-34 yr	157	47	158	55	174	43	138	50	159	29
35-39 yr	143	50	141	36	156	46	141	40	144	57
40-44 yr	121	52	126	45	127	46	138	47	138	36
45-49 yr	138	76	150	76	145	66	150	90	168	76
50-54 yr	144	98	145	107	127	114	152	143	161	129
55-59 yr	175	179	187	210	196	176	193	164	182	202
60-64 yr	246	338	237	328	259	338	252	378	241	357
65-69 yr	408	732	394	724	403	667	415	655	374	690
70-74 yr	640	1,375	629	1,298	604	1,400	648	1,411	659	1,351
75-79 yr	777	2,281	775	2,355	854	2,243	985	2,464	913	2,632
80-84 yr	955	3,262	983	3,312	1,065	3,395	1,121	3,671	1,147	3,490
85+ yr	1,139	4,894	1,180	5,092	1,345	5,496	1,428	5,912	1,477	6,100
not stated		2	1			1				
Total	6,490	13,933	6,633	14,167	6,977	14,524	7,295	15,518	7,299	15,663

Appendix 6 – Worked examples of calculation of pre-treatment fracture rates
Worked examples of calculation of pre-treatment fracture rates at or below treatment threshold Z<-1

Pre-treatment fracture rate for 55 year old women BELOW the treatment threshold of *Z*<-1

Population risk of hip fracture=0.047%

μ =0.881 g/cm^2 (*Z*=-1=0.761 g/cm^2)

σ=0.12

RR=2.6

$$=0.05\% \times \frac{\Phi\left(\frac{0.761 - 0.881}{0.12}\right) - \log_e 2.6}{\Phi\left(\frac{0.761 - 0.881}{0.12}\right)}$$

x by 0.12 → $=0.05\% \times \Phi(0.761 - 0.881) - (\log_e 2.6 \times 0.12)$ / $\Phi(0.761 - 0.881)$

=0.14%

Pre-treatment fracture rate for a 55 year old women AT the treatment threshold *Z*=-1

Population risk of hip fracture=0.05%

μ =0.881 g/cm^2 (*Z*=-1=→ 0.761 g/cm^2)

σ=0.12

RR=2.6

$$=\frac{0.047\% \times \exp[(-\log(2.6) \times (0.761-0.881) - (\log(2.6))^2]}{2}$$

=0.048%

HIP FRACTURE PREVENTION USING ALENDRONATE: TWO MODELS FOR NUMBER NEEDED TO TREAT AND SCREEN

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Number needed to treat (NNT) and needed to screen (NNS) are useful for determining efficacy and scale of disease treatments and screening programs. Hip fractures result in morbidity and mortality, warranting screening for osteoporosis (OST) in high-risk populations. Alendronate (ALN) has been shown to increase bone mineral density (BMD) and reduce fracture (#) rate numerous studies. Modelling analyses are useful, as long-term # studies are difficult to conduct. Modelling studies can provide information for today.

To derive NNS for normal patients subsequently treated with ALN using DEXA to prevent one hip #. (1) A literature derived model using hip # incidence in ALN treated groups, and population BMD data. (2) Markov model including BMD reduction and fracture risk data for COPD (chronic obstructive pulmonary disease) and non-COPD groups, used to determine hip # risk, and treatment responses by gender and initial BMD. (1)Post-menopausal women aged 65-74 years with starting BMD of 0.565±0.07 g/cm^3 (mean, SD)[1], estimated prevalence of OST of 29% in this age group. Control hip # rate of 2.2% over 1 year, vs 1.1% in the treated group, relative risk reduction of 50% and absolute risk reduction of 1.1%. NNT=1/ARR=90; NNS=NNT/underlying prevalence=310. 2) We calculated the ratio of 64-year-old women with COPD treated with ALN for 1 year PHFP. Women with mild OST (Z=-1 → -2 SD's) required 213 women treated PHFP, moderate OST (Z=-2 → -3) 78 women PHFP, and severe OST (Z<-3) 33 women PHFP. For healthy women aged 64 years the numbers are 248, 87, 35.

We estimate that literature derived NNT/NNS calculations are reasonable. Markov modelling shows fewer women aged 64 need to be treated PHFP as BMD rises. Numbers of women treated PHFP does not differ greatly between COPD and normal groups. Further analyses will show if these interventions are cost-effective.

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The Australian Rheumatology Association Conference, Hobart 2000. Poster presentation.

A TOOL FOR IDENTIFYING MEN AND WOMEN WITH RESPIRATORY DISEASE WHO DO NOT REQUIRE BONE DENSITY SCREENING

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Patients with respiratory disease have decreased mean bone mineral density (BMD) and increased risk of bone fractures. Risk factor models poorly predict patients who have low BMD. Therefore, we developed a screening tool to identify patients unlikely to require bone densitometry. A cross-sectional convenience sample (N=239) of patients with respiratory disease was assessed using dual-energy x-ray absorptiometry (DXA) and analysed using multiple stepwise logistic regression. The prevalence of low BMD, defined as a *Z*-score <-1.5 at lumbar spine, neck of femur or total femur, was 21%. Participants with respiratory disease and ALL of: BMI >20; smoked <80 pack years; not currently using warfarin; FEV_1 ≥60% predicted were NOT recommended for DXA, thereby eliminating 35% of participants. The sensitivity, specificity, positive predictive value and negative predictive values were 86, 41, 27 and 92% respectively; area under the ROC curve was 0.7. Our pre-screening tool may assist clinicians to identify those not requiring BMD screening, allowing more effective use of DXA resources.

Australasian Epidemiology Association conference, Sydney 2001.

Poster presentation.

A TOOL FOR IDENTIFYING MEN AND WOMEN WITH RESPIRATORY DISEASE WHO DO NOT REQUIRE BONE DENSITY SCREENING

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Osteoporotic fractures result in high morbidity and mortality. Patients with respiratory disease have decreased mean bone mineral density (BMD) and increased risk of bone fractures, warranting consideration of osteoporosis screening in this patient group. Therefore, we developed a screening tool to identify patients unlikely to require bone densitometry using risk factors selected from the literature.

A cross-sectional convenience sample (N=239) of patients with mild to severe respiratory disease was assessed using dual-energy x-ray absorptiometry (DXA) and analysed using multiple stepwise logistic regression. The prevalence of low BMD, defined as a *Z*-score of <-1.5 at the lumbar spine, neck of femur or total femur, was 21%.

At selected sensitivity of 86%, specificity was 41%, positive predictive value (PPV) was 27%, negative predictive value (NPV) was 92%. The area under the curve was 0.70. Participants with respiratory disease and ALL of: BMI>20; smoked <80 pack years; not currently using warfarin; FEV_1 ≥60% of predicted were NOT recommended for DXA, thereby eliminating 35% of participants.

Our screening tool is moderately informative, easy to administer, and may assist a GP or respiratory physician to identify people with respiratory disease at low risk of osteoporosis who do not require bone density screening with DXA. Specificity and PPV of this tool at stated sensitivity is poor, with many patients recommended for DXA screening having normal BMD. NPV is high, enabling osteoporosis to be confidently excluded in people not recommended for screening DXA. Additional risk factors usually considered predictive of osteoporosis eg prednisolone usage, previous fractures did not add further information regarding risk of low BMD for our data. Our tool excludes one third of our target population, allowing more effective use of the limited resources of DXA. Despite the small proportion of participants not recommended for screening DXA, such programs may prove to be cost-effective when cost of averted fractures is considered.

North West Adelaide Health Service Research Day, 2001. Oral presentation.

NUMBER NEEDED TO SCREEN AND NUMBER NEEDED TO TREAT FOR PREVENTING HIP FRACTURES IN MEN AND WOMEN WITH COPD

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Number needed to screen (NNS) and number needed to treat (NNT) are integral components of today's disease screening programs. Hip fractures cause significant morbidity and mortality, with COPD patients at high risk of sustaining osteoporotic fractures, with bone density (BMD) at 10% below mean for age. Therefore consideration of screening for and treating low BMD in men and women with COPD is warranted. The effect of alendronate (ALN) therapy on BMD and hip fracture rates can be accurately modelled to provide public health data today. NNS and NNT estimates were developed using fracture rates derived from literature equations, and extended over 10 years using Markov simulations and mortality estimates. NNS and NNT for starting ALN treatment in men and women in the general population and with COPD at age 55 and 65 with BMD of 1, 1.5 and 2 standard deviations below age-matched mean (*Z*-score) are tabulated.

		General Population		COPD Population	
Start treatment at age	Treatment decision	NNS Female (male)	NNT Female (male)	NNS Female (male)	NNT Female (male)
55	*Z*<-1	999 (3,044)	159 (483)	381 (1,126)	149 (441)
	Z<-1.5	1,642 (5,008)	110 (335)	508 (1,492)	111 (328)
	Z<-2	3,242 (9,900)	74 (225)	787 (2,297)	80 (234)
65	*Z*<-1	268 (777)	42 (122)	122 (328)	46 (125)
	Z<-1.5	438 (1,276)	29 (84)	165 (440)	34 (93)
	Z<-2	853 (2,512)	19 (56)	259 (687)	24 (66)

The NNS to prevent one hip fracture after 10 years ALN treatment is markedly less in both men and women with COPD and reduces significantly in the elderly and with reducing BMD. Further analyses will show if screening and treatment is cost-effective in these groups.

Supported by the NHMRC. **Key words:** Osteoporosis, number needed to screen, number needed to treat, alendronate, COPD. **Nominations for awards:** None.

Thoracic Society of Australia and New Zealand, Adelaide 2003. Poster presentation.

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