ACE Prevention Briefing Paper no. 5, St Cttee meeting March 2008 (revised)

Fracture prevention among older women by opportunistic bone mineral density measurement in combination with alendronate treatment for osteoporosis

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1.1 Definition of intervention

Opportunistic screening for low bone mineral density (BMD) for women aged 70 to 90 years who present to their GP for an unrelated purpose, and subsequent treatment of those who fall below the threshold for osteoporosis with alendronate (one of the bisphosphonates) 70 mg once weekly, and calcium 500 mg/day, for 5 years. Fig 1 shows the intervention pathway. Substantial uncertainty in various important parameters is examined in a sensitivity analysis. Similar exercises will follow for residronate, raloxifene, the combination of calcium and vitamin D, and physical exercise. All of these analyses will be replicated for men.

1.2 Health states/risk factors affected by the intervention

Therapy aims to reduce fractures of the hip, spine (vertebrae), pelvis, clavicula/humerus (shoulder / upper arm), rib, wrist, hand, lower leg, foot.

1.3 Current Practice

Recently about 15% of the women aged 70-90 years with osteoporosis received pharmaceutical treatment, of which 75% was a bisphosphonate. This estimate is based on a study by Chiang et al[1] which reported on the percentage of men and women with osteoporosis that used any drugs for osteoporosis, and PBS data from which we calculate each class of drug's contribution to the percentage of women on treatment, by age. The effectiveness of the drugs in preventing fractures for each fracture site is estimated based on meta-analyses. Since 2008, the PBS subsidises alendronate for women with osteoporosis aged 70 and over without a previous fracture. This study estimates the cost-effectiveness of that measure.

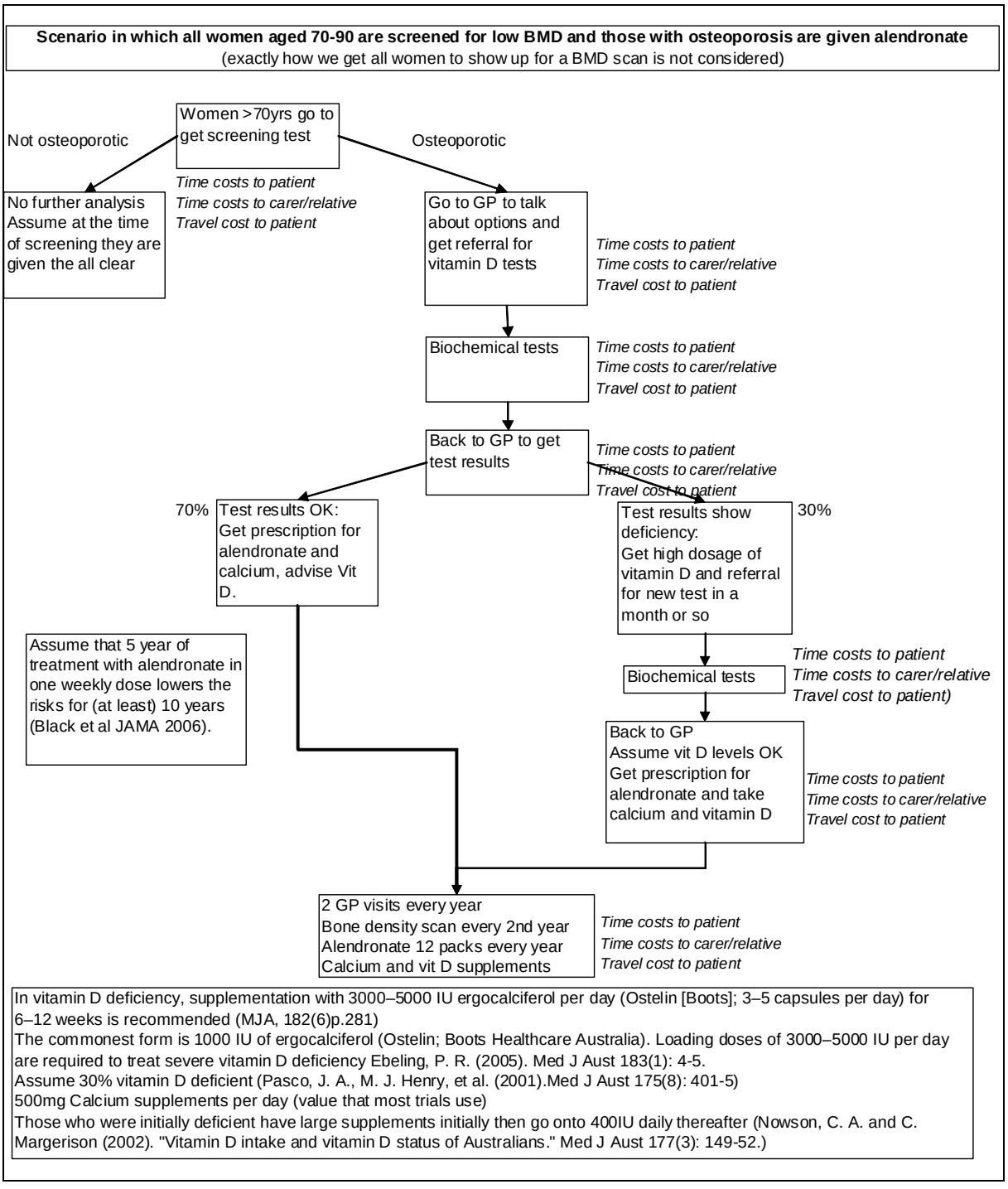

Fig. 1. The intervention pathway.

1.4 Efficacy/Effectiveness of intervention/s

We used relative risks (RRs) from a recent Cochrane review[2] for hip and spine fractures, and those from Stevenson et al[3] for the other fractures types. We corrected the RRs for an average adherence in the trials of 78%, and assumed 59% of those screened adhere to the

drug.[4] Treatment is assumed to last for 5 years, and the effect is modelled to last for 5 additional years.[5] We arbitrarily assumed a random 33% of the target group participates in the screening programme. The participation rate has no influence on cost-effectiveness ratios but would affect total costs and total health gain estimates.

1.5 Modelling to health outcomes

Based on population distributions of BMD, relative risks for fracture by BMD and age, and treatment as described above, the model estimates a change in the incidence of fractures due the screening program and subsequent drug treatment. The health impact of different fractures is measured in a multi-state life table. All effects and costs are linked to the number of incident cases, by age, except for hip fractures which also have long-term disability. Results are obtained separately for 5-year age groups and then added up.

The population distribution of BMD by age is fitted to data from the Geelong and Dubbo studies.[6] [7] The threshold for osteoporosis has been defined on the same data, using the WHO definition (a BMD that is lower than 2.5 standard deviations below the mean for 25-year old women). In combination with age- and BMD level-specific fracture relative risks[8], this allows calculation of the average fracture risk for women with osteoporosis. This risk is lowered for the proportion of women at each age that use alendronate. Before estimating the number of fractures that are prevented, the effect of current treatment is removed by the same procedure in reverse, which leads to a slightly higher fracture incidence ("partial null scenario").

Incidence and mortality of fractures were estimated in the Australian Burden of Disease 2003. Mortality was observed for fractures of the hip (85% of the total number of osteoporotic deaths), pelvis, clavicle, rib and spine, and was assumed to occur within a year after fracture. In addition, survivors of a hip fracture cases are exposed to a 20% increased risk of death.[9] Hip fracture cases have a 29% chance of long-term disability with severity estimated at a disability weight level of 0.272 (systematic review done as part of Aus BoD), of which half is attributed to osteoporosis and half to pre-existing frailty. The latter assumption is not based on evidence and varied in the sensitivity analysis. The model assumes that about 2% of people on alendronate use ranitidine for gastro-intestinal complaints.[10]

The present analysis does not (yet) include the effect of osteonecrosis of the jaw that occurs in 0.01% to 0.04% of users, or the costs of dental consultation to prevent this complication.[11]

1.6 Costs of interventions and offsets

Costs of the intervention were as per ACE economic protocol. Costs of health care were based on the Medicare Benefit Schedule. Cost offsets in the first year post-fracture were based on the Dubbo study.[12] We found no evidence for the long-term costs following hip fractures. In a sensitivity analysis a cost of $5,000 per year is attributed to persons with long-term disability.

1.7 Uncertainty analysis

Parameter	Values	Uncertainty distribution	Source
Risk by level of BMD	Variable by age and BMD-level; see appendix.	Normal	Data[8] provided by prof. Kanis.
Efficacy hip	0.32 (0.18-0.58)	Normal around log RR	Meta-analysis[2] (corrected for adherence)
Efficacy spine	0.42 (0.35-0.52)	Normal around log RR	Meta-analysis[2] (corrected for adherence)
Efficacy forearm/wrist	0.36 (0.24-0.53)	Normal around log RR	Meta-analysis[2] (corrected for adherence)
Efficacy other osteoporotic fractures	0.83 (0.68-1.02)	Normal around log RR	Meta-analysis[2] (corrected for adherence)
Proportion hospitalised	Varies by fracture site	Beta	Dubbo study[12]
Cost-offsets	Varies by fracture site. (Hip $20,000)	Gamma	Dubbo study[12]
Ranitidine 150 mg/day (for GI side effects)	2.0% (0.9 – 3.2)	Normal	[10, 13]
Vit. D supplementation	4 (3,5) Caps/wk	Uniform	[13]
Weeks of Vit. D	9 (6,12)	Uniform	[13]

Alendronate	$729 per year	None	PBS, Nov. 2003
BMD screening	$85.05	None	MBS Nov. 2003
Test for vit D deficiency	$55.90	None	MBS Nov. 2003

1.8 Results and Sensitivity Analysis

	Median	95% uncertainty interval
years of life saved	6,900	4,000 to 8,700
DALYs averted	8,600	5,000 to 10,800
cost intervention (million $)	312	310 to 313
net costs (million $)	36	-315 to 200
ICER with cost-offsets	$4,400	cost-saving to 34,000
ICER without cost-offsets	$36,000	29,000 to 62,000

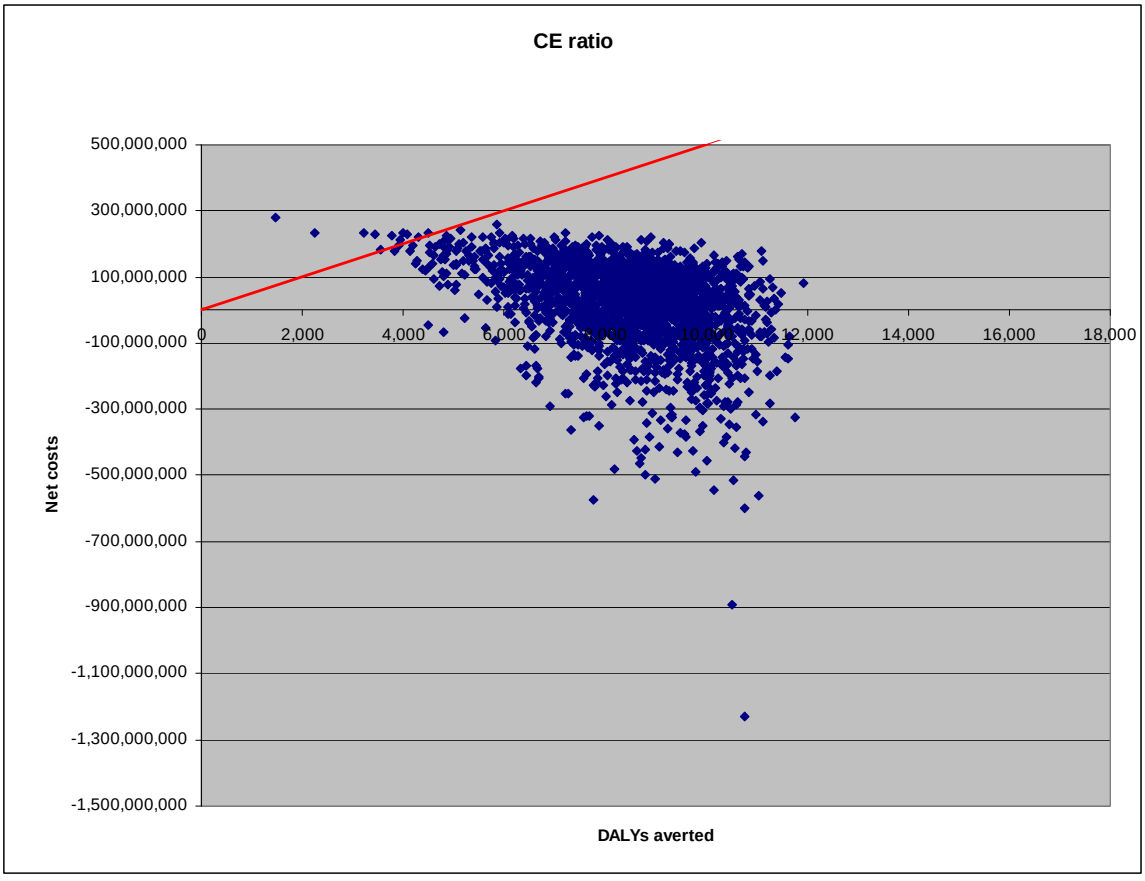

Fig. 2: Cost-effectiveness plane of base case scenario. The red diagonal line depicts the $50,000 / DALY cut-off.

We examined the effects of the most significant factors that introduce uncertainty in this analysis (fig. 3).

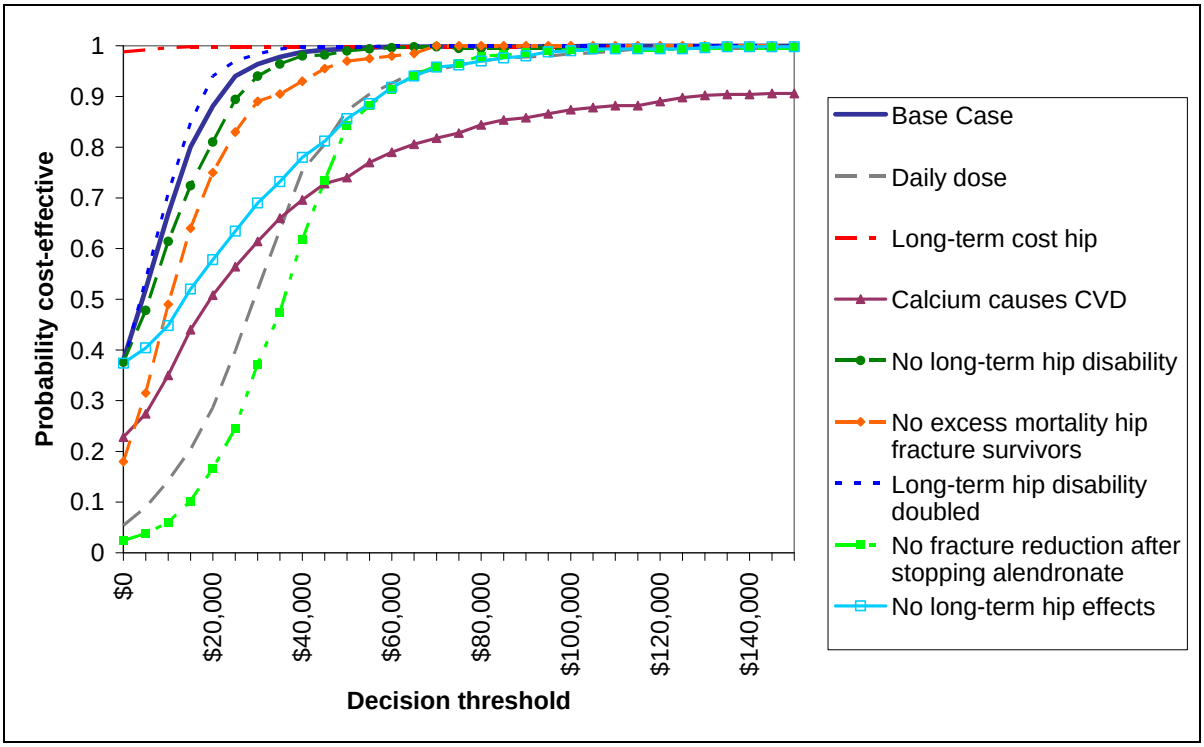

Fig. 3. Cost-effectiveness acceptability curve with results of the one-way sensitivity analysis.

The use of alendronate in a daily rather than weekly dose significantly worsens cost-effectiveness, because it reduces adherence from 59% to 15%.[4] The daily dose is not subsidised by PBS. Varying the amount of long-term disability in hip fracture survivors (double or none) has little effect. Reducing their excess mortality (20% in the base case) to the average for age and sex worsens cost-effectiveness, but the intervention has an 85% chance of being cost-effective at the $50,000 level even if no long-term effects of hip fractures (mortality, morbidity nor cost-offsets) are taken into account. The base case analysis includes no extra costs for women with long-term disability due to hip fractures. Adding an arbitrary $5,000 per year greatly improves cost-effectiveness, but important questions remain whether these costs are realistic and whether they should be attributed to osteoporosis or to pre-existing frailty. Assuming that alendronate only reduces fracture risk while it is taken also worsens cost-effectiveness, but this is an unlikely scenario.

1.9 Discussion

At the $50,000 per DALY level, screening women aged 70 to 90 for low BMD and offering treatment with alendronate in the weekly dose is likely to be cost-effective. This effect is sensitive to adherence, to the possible increased risk of cardiovascular disease associated with calcium supplementation and to long-term costs of hip fractures. And, by extension, to the attribution of long-term consequences of osteoporotic fractures to osteoporosis or to pre-existing frailty. To the extent that participation and adherence is better among the higher educated, the intervention might increase socio-economic inequality. It is medicalising rather than empowering. If 33% of the current cohort of women aged 70-90 were to participate in the first year, the total direct cost would be about $310 million. In reality, this group will be screened over the years, and after an initial peak annual costs will be considerably lower. A possible increase of the risk of heart disease and stroke can be considered an ethical constraint. Feasibility depends mainly on capacity for BMD-scanning. The intervention has already been implemented.

1.10 References

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1.11 Second stage filter analysis summary (appendix)

Table 1: Second stage filter summary

Cost per DALY	Strength of evidence	Equity	Acceptability	Feasibility	Sustainability	Relevance to indigenous population	'other effects' (not captured in modelling)
- cost offsets: $36,000 **+ cost offsets:** $4,400	Good evidence efficacy; weaker evidence on long-term effects and costs of hip fractures and effect of Calcium suppletion	Potential to increase inequities due to differential uptake by socio-economic position	Issues include: None; participation is voluIntary	Issues include: Depends on capacity for BMD scans (including personnel)	Issues include: None	Lower because lower life expectancy; higher because of smoking	Positive: Negative:
Decision point:	additional data desirable but in sensitivity analyses: no change in conclusions						
Policy Considerations:							

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APPENDIX: relative risks by BMD level

z-score of femoral neck

The same cohort as in the paper: Predictive value of BMD for hip and other fracture.

Poisson model: 1. constant, 2. current time, 3. current age, 4. BMD z-score, 5. age x BMD z-score, 6. BMD z-score x BMD z-score

RR (95% confidence interval)

Men+Women, Outcome: hip fracture

Age	-3	-2	-1	0	1	2	3
50	3.35(2.24, 5.00)	3.25(2.24, 4.73)	3.17(2.13, 4.70)	3.08(1.95, 4.88)	3.00(1.73, 5.20)	2.92(1.51, 5.65)	2.84(1.30, 6.18)
55	3.11(2.21, 4.38)	3.03(2.23, 4.12)	2.95(2.11, 4.11)	2.87(1.91, 4.31)	2.79(1.68, 4.64)	2.72(1.45, 5.07)	2.64(1.25, 5.59)
60	2.90(2.19, 3.84)	2.82(2.23, 3.58)	2.75(2.10, 3.59)	2.67(1.87, 3.82)	2.60(1.62, 4.16)	2.53(1.40, 4.58)	2.46(1.19, 5.07)
65	2.70(2.16, 3.37)	2.63(2.23, 3.09)	2.56(2.08, 3.15)	2.49(1.82, 3.40)	2.42(1.56, 3.75)	2.35(1.33, 4.16)	2.29(1.13, 4.62)
70	2.51(2.13, 2.97)	2.45(2.27, 2.64)	2.38(2.05, 2.76)	2.32(1.76, 3.05)	2.25(1.49, 3.40)	2.19(1.27, 3.80)	2.13(1.07, 4.24)
75	2.34(2.07, 2.64)	2.28(2.14, 2.34)	2.22(2.02, 2.43)	2.16(1.68, 2.77)	2.10(1.41, 3.12)	2.04(1.19, 3.49)	1.99(1.01, 3.91)
80	2.18(1.97, 2.41)	2.12(1.99, 2.26)	2.06(1.94, 2.20)	2.01(1.57, 2.56)	1.95(1.32, 2.89)	1.90(1.12, 3.24)	1.85(0.94, 3.63)
85	2.03(1.81, 2.28)	1.97(1.85, 2.10)	1.92(1.76, 2.10)	1.87(1.46, 2.40)	1.82(1.23, 2.70)	1.77(1.04, 3.02)	1.72(0.88, 3.39)

Men+Women, Outcome: osteoporotic fracture without hip fracture

Age	-3	-2	-1	0	1	2	3
50	1.37(1.09, 1.73)	1.30(1.08, 1.55)	1.23(1.07, 1.41)	1.16(1.03, 1.31)	1.10(0.95, 1.27)	1.04(0.86, 1.25)	0.98(0.78, 1.25)
55	1.41(1.13, 1.76)	1.33(1.13, 1.58)	1.26(1.12, 1.43)	1.20(1.08, 1.33)	1.13(1.00, 1.28)	1.07(0.90, 1.27)	1.01(0.81, 1.27)
60	1.45(1.17, 1.80)	1.37(1.18, 1.61)	1.30(1.17, 1.45)	1.23(1.13, 1.34)	1.16(1.04, 1.30)	1.10(0.94, 1.30)	1.04(0.83, 1.30)
65	1.49(1.21, 1.84)	1.41(1.22, 1.64)	1.34(1.21, 1.47)	1.27(1.17, 1.36)	1.20(1.08, 1.33)	1.13(0.97, 1.32)	1.07(0.86, 1.33)
70	1.54(1.25, 1.89)	1.45(1.25, 1.69)	1.38(1.25, 1.51)	1.30(1.21, 1.40)	1.23(1.12, 1.36)	1.17(1.00, 1.36)	1.10(0.89, 1.37)
75	1.58(1.28, 1.95)	1.50(1.29, 1.74)	1.42(1.28, 1.56)	1.34(1.24, 1.45)	1.27(1.14, 1.41)	1.20(1.03, 1.40)	1.14(0.91, 1.41)
80	1.63(1.31, 2.02)	1.54(1.32, 1.80)	1.46(1.31, 1.63)	1.38(1.26, 1.51)	1.30(1.16, 1.46)	1.23(1.05, 1.45)	1.17(0.93, 1.46)
85	1.67(1.34, 2.10)	1.58(1.34, 1.88)	1.50(1.32, 1.70)	1.42(1.27, 1.58)	1.34(1.18, 1.53)	1.27(1.07, 1.51)	1.20(0.95, 1.51)