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Abstract

The implications of competing risks and direct treatment disutility in cardiovascular disease and osteoporotic fracture: risk prediction and cost effectiveness analysis

Bruce Guthrie,[1*] Gabriel Rogers,[2] Shona Livingstone,[3] Daniel R Morales,[3] Peter Donnan,[3] Sarah Davis,[4] Ji Hee Youn,[5] Rob Hainsworth,[2] Alexander Thompson[2] and Katherine Payne[2]

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Background: Clinical guidelines commonly recommend preventative treatments for people above a risk threshold. Therefore, decision-makers must have faith in risk prediction tools and model-based cost-effectiveness analyses for people at different levels of risk. Two problems that arise are inadequate handling of competing risks of death and failing to account for direct treatment disutility (i.e. the hassle of taking treatments). We explored these issues using two case studies: primary prevention of cardiovascular disease using statins and osteoporotic fracture using bisphosphonates.

Objectives: Externally validate three risk prediction tools [QRISK®3, QRISK®-Lifetime, QFracture-2012 (ClinRisk Ltd, Leeds, UK)]; derive and internally validate new risk prediction tools for cardiovascular disease [competing mortality risk model with Charlson Comorbidity Index (CRISK-CCI)] and fracture (CFracture), accounting for competing-cause death; quantify direct treatment disutility for statins and bisphosphonates; and examine the effect of competing risks and direct treatment disutility on the cost-effectiveness of preventative treatments.

Design, participants, main outcome measures, data sources: Discrimination and calibration of risk prediction models (Clinical Practice Research Datalink participants: aged 25–84 years for cardiovascular disease and aged 30–99 years for fractures); direct treatment disutility was elicited in online stated-preference surveys (people with/people without experience of statins/bisphosphonates); costs and quality-adjusted life-years were determined from decision-analytic modelling (updated models used in National Institute for Health and Care Excellence decision-making).

Results: CRISK-CCI has excellent discrimination, similar to that of QRISK3 (Harrell's *c* = 0.864 vs. 0.865, respectively, for women; and 0.819 vs. 0.834, respectively, for men). CRISK-CCI has systematically better calibration, although both models overpredict in high-risk subgroups. People recommended for treatment (10-year risk of ≥ 10%) are younger when using QRISK-Lifetime than when using QRISK3, and have fewer observed events in a 10-year follow-up (4.0% vs. 11.9%, respectively, for women; and 4.3% vs. 10.8%, respectively, for men). QFracture-2012 underpredicts fractures, owing to under-ascertainment of events in its derivation. However, there is major overprediction among people aged 85–99 years and/or with multiple long-term conditions. CFracture is better calibrated, although it

also overpredicts among older people. In a time trade-off exercise (n = 879), statins exhibited direct treatment disutility of 0.034; for bisphosphonates, it was greater, at 0.067. Inconvenience also influenced preferences in best–worst scaling (n = 631). Updated cost-effectiveness analysis generates more quality-adjusted life-years among people with below-average cardiovascular risk and fewer among people with above-average risk. If people experience disutility when taking statins, the cardiovascular risk threshold at which benefits outweigh harms rises with age (≥ 8% 10-year risk at 40 years of age; ≥ 38% 10-year risk at 80 years of age). Assuming that everyone experiences population-average direct treatment disutility with oral bisphosphonates, treatment is net harmful at all levels of risk.

Limitations: Treating data as missing at random is a strong assumption in risk prediction model derivation. Disentangling the effect of statins from secular trends in cardiovascular disease in the previous two decades is challenging. Validating lifetime risk prediction is impossible without using very historical data. Respondents to our stated-preference survey may not be representative of the population. There is no consensus on which direct treatment disutilities should be used for cost-effectiveness analyses. Not all the inputs to the cost-effectiveness models could be updated.

Conclusions: Ignoring competing mortality in risk prediction overestimates the risk of cardiovascular events and fracture, especially among older people and those with multimorbidity. Adjustment for competing risk does not meaningfully alter cost-effectiveness of these preventative interventions, but direct treatment disutility is measurable and has the potential to alter the balance of benefits and harms. We argue that this is best addressed in individual-level shared decision-making.

Study registration: This study is registered as PROSPERO CRD42021249959.

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List of abbreviations

ADE	adverse drug event
AIC	Akaike information criterion
AUROC	area under the receiver operating curve
BMI	body mass index
BWS	best–worst scaling
CCI	Charlson Comorbidity Index
CEA	cost-effectiveness analysis
CG181	Clinical Guideline 181
CI	confidence interval
CKD	chronic kidney disease
CPRD	Clinical Practice Research Datalink
CRISK	competing mortality risk model
CRISK-CCI	competing mortality risk model with Charlson Comorbidity Index
CVD	cardiovascular disease
DTD	direct treatment disutility
eGFR	estimated glomerular filtration rate
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
GAM	generalised additive model
GP	general practitioner
HES	Hospital Episode Statistics
HR	hazard ratio
HSE	Health Survey for England
HTA	Health Technology Assessment
ICD-10	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision
ICER	incremental cost-effectiveness ratio
mCCI	modified Charlson Comorbidity Index
MI	myocardial infarction
MOF	major osteoporotic fracture
MSE	minor side effect
NHB	net health benefit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NNT	number needed to treat
ONS	Office for National Statistics
OR	odds ratio
PAD	peripheral arterial disease
PICOS	population, intervention, comparator, outcome, study type
QALY	quality-adjusted life-year
QS149	Quality Standard 149
SA	stable angina
SBP	systolic blood pressure
SE	standard error
SHARE	Scottish Health Research Register
SSE	severe side effect
TA464	Technology Appraisal 464
TC : HDL	total cholesterol: high-density lipoprotein ratio
TIA	transient ischaemic attack
TTO	time trade-off
UA	unstable angina

Plain language summary

Before offering a medicine to prevent disease, prescribers must expect it to do more good than harm. This balance depends on how likely it is that the person will develop the disease we want to prevent. But people might first die for other reasons. We call this a 'competing risk'. In most cases, the mathematical tools we use to estimate the chance of developing a disease do not account for competing risks. Another problem is that, when weighing up the benefits and harms of medicines, we ignore the hassle they cause patients, even when they do not cause side effects.

We used two examples: statins to prevent heart disease and bisphosphonates to prevent fractures. First, we assessed if existing tools get predictions wrong by not accounting for competing risks. We found that they exaggerate the chance of heart attacks and strokes. However, the exaggeration is greatest among people who would clearly benefit from preventative treatment. So it may not change treatment decisions much. The fracture prediction tool we studied was very inaccurate, exaggerating risk among older people, but underestimating risk among younger people. We made a new fracture risk prediction tool. It gave better predictions, but it was still inaccurate for people aged > 85 years and those with several health problems.

Next, we asked people questions designed to put a number on the hassle that statins and bisphosphonates cause. Most people thought that taking either is inconvenient, but the hassle factor for bisphosphonates is bigger.

Finally, we updated the mathematical models that the National Institute for Health and Care Excellence used when recommending statins and bisphosphonates. We worked out if competing risks and the hassle of taking medicines make a difference to results. Statins remain a good idea for almost everyone, unless they really hate the idea of taking them. But bisphosphonates would do more harm than good for anyone who agrees with the hassle factor we found.

Scientific summary

Background

Clinical guidelines help define and disseminate best practice. Guidelines increasingly use risk prediction tools to help target primary preventative treatments at people at highest risk. In National Institute for Health and Care Excellence (NICE) guidelines, the choice of risk threshold is commonly informed by model-based cost-effectiveness analyses (CEAs) for different levels of baseline risk. Risk prediction modelling and model-based CEA are therefore increasingly important for developing guidelines that recommend long-term preventative medicines, including primary prevention of cardiovascular disease (CVD) using statins and prevention of osteoporotic fracture using bisphosphonates.

Risk prediction and competing mortality risk

Most risk prediction models do not account for competing mortality risk, which is when someone dies of another condition (e.g. lung cancer) before experiencing the event being predicted (e.g. CVD or fracture). This can lead to overprediction of event rates among older people and those with multimorbidity.

Model-based cost-effectiveness analysis

Competing mortality risk is accounted for in model-based CEA, but whole-population estimates of competing mortality will not be correct at all levels of risk of CVD and fracture. Existing models also do not account for all harms, notably direct treatment disutility (DTD), which is the disutility arising from the hassles of taking treatments. Even small levels of DTD can be enough to outweigh relatively small lifetime benefits of primary prevention medication, but, to our knowledge, DTD impact has not been systematically estimated previously.

Aim and objectives

The overall aim was to improve the evidence generated from risk prediction models and model-based CEAs to inform decision-making for selecting primary prevention treatments for CVD and osteoporotic fracture.

The prespecified objectives were to:

1. externally validate the recommended risk prediction tools for primary prevention of CVD [QRISK®3 (ClinRisk Ltd, Leeds, UK)] and for osteoporotic fracture [QFracture-2012 (ClinRisk Ltd)]
2. derive and internally validate new CVD and osteoporotic fracture risk prediction models accounting for competing risks of death
3. externally validate the QRISK-Lifetime CVD risk prediction tool
4. quantify the magnitude, variation and distribution of DTD in the general population and among people treated with statins or bisphosphonates
5. examine the effect of accounting for competing risks and DTD on cost-effectiveness in the context of statins and bisphosphonates for the primary prevention of CVD and osteoporotic fracture, respectively.

The prediction modelling protocol was approved by the Clinical Practice Research Datalink (CPRD) Independent Scientific Advisory Committee (reference number 16_248). The Health Research Authority approved the DTD elicitation study (Integrated Research Application System: 220,492) and granted ethics approval (Research Ethics Committee: 17/NW/0124). A systematic review for CEA model parameters was registered with PROSPERO (CRD42021249959).

Methods

Objective 1 methods

For CVD modelling, CPRD GOLD data were used to define a cohort aged 25–84 years without CVD or prior statin prescription. The outcome was incident CVD. Multiple imputation was used to account for missing data. The performance of the published QRISK3–2017 model was evaluated in terms of discrimination (the ability of a tool to distinguish between those with and those without an event) and calibration (whether or not predicted risk is the same as observed risk) in the whole population, stratified by age and Charlson Comorbidity Index (CCI), and in subgroups with type 1 diabetes, type 2 diabetes and chronic kidney disease (CKD). Observed risk was estimated with and without accounting for competing risk (using Aalen–Johansen and Kaplan–Meier estimators, respectively).

For fracture modelling, the cohort was aged 30–99 years (prior fracture or bisphosphonate treatment were allowed) with follow-up to specified fracture, death from non-fracture causes, deregistration or end of study. Two outcomes were defined: major osteoporotic fracture (MOF) and hip fracture. QFracture-2012 performance was evaluated as for QRISK3.

For both cohorts, the earliest study entry date was 1 January 2004 and the end of the study was 31 March 2016.

Objective 2 methods

Using the same data set as objective 1, participants were randomly allocated to derivation and test data sets in a 2 : 1 ratio. For CVD, two Fine–Gray models were derived in the derivation data set and internally validated in the test data set, alongside QRISK3. The competing mortality risk model (CRISK) accounted for competing mortality only, whereas the competing mortality risk model with Charlson Comorbidity Index (CRISK-CCI) also included the modified CCI as a predictor. Model performance was examined using discrimination and calibration. For fracture, separate Fine–Gray models (CFracture) were estimated for MOF and hip fracture.

Objective 3 methods

The same data were used as for objective 1, but with the age range restricted to 30–84 years to match QRISK®-Lifetime (ClinRisk Ltd). As lifetime risk is not observed in this data set, model performance was evaluated at 10 years, and reclassification examined the characteristics of those recommended for treatment on the basis of a QRISK3 10-year risk of > 10%, a QRISK-Lifetime 10-year risk of > 10% and the QRISK-Lifetime highest risk, with thresholds chosen to recommend the same number of people for treatment as with QRISK3 > 10%.

Objective 4 methods

Two groups of participants were recruited to studies to elicit DTD of preventative statins and bisphosphonates: people with direct experience of taking one of the medicines and a sample of the general population. We described the process of taking each medicine (one tablet per day for statins, one tablet per week taken on an empty stomach with a requirement to stay upright for at least 30 minutes for bisphosphonates). Elicitation used time trade-off (TTO) (primary analysis) and best–worst scaling (BWS) (exploratory analysis) surveys iteratively developed using think-aloud interviews with 19 patients, and online pilot studies.

Objective 5 methods

For statins for the primary prevention of CVD, we modified the cohort-level decision-analytic model used in NICE's lipid modification guideline [NICE. *Lipid Modification: Cardiovascular Risk Assessment and the Modification of Blood Lipids for the Primary and Secondary Prevention of Cardiovascular Disease. Clinical Guideline (CG181). Methods, Evidence and Recommendations. July 2014*. URL: https://web.archive.org/web/20220201050407/https://www.nice.org.uk/guidance/cg181/evidence/lipid-modification-update-full-guideline-pdf-243786637 (accessed 12 October 2022)]. General updates included rapid reviews to

identify utility values and costs associated with CVD events, new regressions to predict baseline quality of life for people without CVD (based on Health Survey for England data) and type of first CVD event (based on data from objective 1), and inputs (costs, life expectancy) were updated to present-day values. For bisphosphonates for the prevention of fracture, we used the discrete-event simulation developed for NICE's Technology Appraisal 464 [NICE. *Bisphosphonates for Treating Osteoporosis. Technology Appraisal Guidance (TA464).* London: NICE; 2017].

For both models, we explored competing risk by parameterising probability of non-cause-specific death using relative survival models adjusting for predicted risk (QRISK3 or QFracture-2012). We incorporated DTD as elicited in objective 4 under three assumptions (lifelong, time limited, diminishing over time). We explored how these factors alone or in combination affect the estimated value of the preventative medicines in terms of cost per quality-adjusted life-year (QALY).

Results

Objectives 1 and 2: predicting cardiovascular disease

Discrimination of QRISK3 in the whole external validation cohort was excellent (Harrell's *c* = 0.865 for women, 0.834 for men), and comparable to the previous internal validation. However, discrimination was worse among people with more comorbidity, and was poor to moderate among older people (e.g. *c* = 0.611 for women and 0.585 for men aged 75–84 years). Calibration in the whole population, ignoring competing risks, was very good, with minor overprediction. There was larger overprediction among older people, which was considerable after accounting for competing risks.

Among people with type 1 diabetes, discrimination was excellent (*c* = 0.830 for women, 0.853 for men). There was evidence of overprediction at higher levels of predicted risk, which was larger after accounting for competing risks, although most overprediction happened well above the NICE 10% threshold for offering treatment. Discrimination among people with CKD was only moderate (women, *c* = 0.705; men, *c* = 0.671), but calibration was reasonable at recommended treatment thresholds.

The new competing risk model (CRISK-CCI) had similar discrimination to QRISK3 in the whole population (women, *c* = 0.864; men, *c* = 0819), with the same pattern of worse discrimination among older people and those with more comorbidity. Calibration was systematically better than QRISK3, although, as with QRISK3, there was overprediction in some subgroups with high predicted risk.

Objectives 1 and 2: predicting fracture

Observed age-stratified incidences of both MOF and hip fracture were considerably higher in this study than in a previous external validation, which was partly explained by the use of hospital data in this study to ascertain fractures. Discrimination of QFracture-2012 in external validation was excellent among women (MOF, *c* = 0.813; hip fracture, *c* = 0.918) and good to excellent among men (MOF, *c* = 0.738; hip fracture, *c* = 0.888), similar to QFracture-2012 internal validation, but had poor to moderate discrimination among older people. Ignoring competing risks, QFracture-2012 showed serious underprediction in the whole population and in all subgroups of age and comorbidity, which was worse for hip fracture than for MOF. Accounting for competing risks reduced observed underprediction in the whole population, but there was very major overprediction among older people and at higher levels of predicted risk among people with more comorbidity.

The new competing risk model (CFracture) had similar discrimination to QFracture-2012 in the internal validation cohort (women: *c* = 0.813 for MOF, *c* = 0.914 for hip fracture; men: *c* = 0.734 for MOF, *c* = 0.883 for hip fracture). CFracture was better calibrated than QFracture-2012 but showed overprediction at higher levels of predicted risk for MOF (both sexes) and for hip fracture (among men). CFracture calibration was poor among people aged 85–99 years for both outcomes.

Objective 3: predicting lifetime cardiovascular disease risk

Evaluated at 10 years' follow-up, QRISK-Lifetime had excellent discrimination (women, *c* = 0.844; men, *c* = 0.808) in the whole population, with the same pattern as QRISK3 and CRISK-CCI of worse discrimination among older people and those with high comorbidity. QRISK-Lifetime underpredicted 10-year risk among people at higher predicted risk, particularly older people, implying that estimated lifetime risk will be underpredicted. A total of 5.3% of participants were recommended for treatment by both QRISK3 and QRISK-Lifetime, and 27.4% by one or the other, but not both. Participants recommended for treatment by QRISK-Lifetime were younger than those recommended by QRISK3 (mean age: women, 50.5 vs. 71.3 years, respectively; men, 46.3 vs. 63.8 years, respectively), were much more likely to have a strong family history of CVD (women: 36.3% vs. 6.3%, respectively; men: 20.0% vs. 7.2%, respectively) and had many fewer observed events during the 10-year follow-up (women with a CVD event: 4.0% vs. 11.9%, respectively; men with a CVD event: 4.3% vs. 10.8%, respectively).

Objective 4: direct treatment disutility elicitation

When measured by TTO, long-term statin use was associated with mean DTD of 0.034 among people willing to take statins; the equivalent number for bisphosphonates was significantly greater, at 0.067. The findings from the BWS experiment had face validity in that inconvenience influenced preferences. However, the estimated values for DTD are implausibly large.

Consistent with previous studies, these findings suggest three distinct preference phenotypes: some people would avoid taking the medicines at all costs, some people see no problem with them and some people are willing to trade length of life to avoid treatment. The first group are unlikely to initiate treatment and the second group do not anticipate DTD; in the third group, depending on the individual's strength of preference to avoid treatment and the magnitude of expected QALY gains from prevention, DTD may imply that a preventative medicine's negative characteristics outweigh its benefits.

Objective 5: model-based cost-effectiveness analysis

General updates to the CVD model made high-intensity statins more cost-effective for primary prevention. Introducing accurate adjustment for competing risk of non-CVD death had the expected effect: more QALYs among people with below-average CVD risk for their sex and age (who experience lower rates of other-cause mortality) and fewer QALYs among people with above-average risk (whose non-CVD life expectancy is attenuated). However, the impact on incremental cost-effectiveness is minor, and statins remain almost universally cost-effective. Incorporating DTD has a more obvious effect, especially when we assume that it applies undiminished for as long as people take statins for primary prevention. Under that circumstance, the threshold at which expected long-term benefits outweigh DTD-related harm rises with age: for a 40-year-old, a 10-year risk of ≥ 8% would be enough to make treatment net beneficial whereas, for an 80-year-old, that figure rises to 38%.

The model assessing bisphosphonates for the primary prevention of osteoporotic fragility fracture shows that we overestimate value for money among people at the highest risk if we do not adjust for competing risk of non-fracture death. However, this generally affects only the magnitude of expected net benefit among people for whom some degree of benefit is expected. Even among people at highest risk of fracture, average QALY gains associated with bisphosphonates are small and swamped by DTD of any duration. Consequently, it is impossible to identify any group of people for whom oral bisphosphonates represent an effective use of NHS resources, if we assume population-level average DTD for everyone to whom the decision applies.

Conclusions

Implications for healthcare

Ignoring competing mortality in risk prediction overestimates the risk of CVD and fracture among older people and those with multimorbidity, which will lead to overestimation of the benefits of treatment.

This affects fracture risk prediction more than CVD because CVD is a more substantial proportion of total mortality. The QFracture-2012 prediction tool simultaneously underestimates fracture risk among people without high competing mortality risk, partly because it did not include fractures recorded only in hospital data in its derivation. CVD and fracture risk prediction are improved by accounting for competing mortality risks, and transparency of the tools would be improved by fully publishing the codes used to define events and predictors.

We have demonstrated an effective method of making accurate adjustment for competing risk of non-cause-specific death in decision-analytic CEAs. Although it made relatively little difference to the estimated cost-effectiveness of preventative interventions in the examples we explored, we have shown that it could potentially be important. Therefore, we recommend that modellers consider this issue when designing analyses of preventative treatments.

Although we have demonstrated that DTD exists and has the potential to alter the balance of benefits and harms for preventative treatments, we do not recommend that population-level average DTD is incorporated in base-case CEAs. Rather, we recommend that decision-makers review scenarios with and scenarios without DTD and highlight its possible impact, enabling prescribers to engage in shared decision-making that gives appropriate weight to individual preferences.

Research recommendations

The excellent discrimination of QRISK3 and QFracture-2012 arises from including a very broad range of ages, but discrimination and calibration in subgroups are less good. Comparing models created in smaller age groups with whole-population models would be useful. Mortality is only one competing risk, and older people and those with multimorbidity are at risk of many different events. It is important to develop models that better account for multiple important events.

Cost-effectiveness analysis of statins for the primary prevention of CVD could usefully be further modified to (1) enable stratification according to specific coexisting long-term conditions, (2) account for likely adherence to statins in practice and (3) update secondary transitions reflecting the subsequent natural history of CVD among people experiencing events.

Future CEAs of bisphosphonates for the primary prevention of osteoporotic fragility fracture should explore different fracture risk prediction models, and use those based on demonstrable good ascertainment of fractures and accounting for competing mortality risk.

Study registration

This study is registered as PROSPERO CRD42021249959.

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Chapter 1 Background to the project

Clinical guidelines are an important mechanism for defining and disseminating best practice, but are typically created for single conditions and based on evidence from trials that often exclude people with multimorbidity.[1–3] However, the majority of people with long-term conditions have multiple conditions, and the application of single-disease guidelines to people with multimorbidity can be problematic.[1,4–8] A common situation in which this is the case is the use of medicines to prevent future disease, whereby treatment is usually long term, often lifelong. The net expected benefit from such preventative treatments is often relatively small over the period examined in trials, and targeting treatment to those with the most to gain is important. Although trials are almost always done in highly selected populations,[9] the standard assumption is that the relative risk reduction as a result of treatment is constant across the whole clinical population. If this assumption is true, then a major determinant of an individual's expected benefit is their baseline risk of the outcome being prevented. Therefore, guidelines increasingly make risk-stratified treatment recommendations, whereby a risk prediction tool is recommended to estimate the risk of the outcome of choice, and preventative treatment is recommended for those above a particular risk threshold. The choice of risk threshold by the guideline development group is commonly informed by model-based cost-effectiveness analyses (CEAs), which examine cost-effectiveness for different levels of baseline risk. Risk prediction modelling and model-based CEAs are therefore increasingly important in the creation of guidelines that recommend long-term preventative medicines.

Risk prediction models, competing mortality risk and multimorbidity

Cardiovascular disease (CVD) and osteoporotic fracture are two contexts in which the National Institute for Health and Care Excellence (NICE) recommend the use of risk prediction tools to inform decisions about who should receive preventative drug treatment.[10–13] For the primary prevention of CVD using statins, NICE currently recommends the QRISK®2 risk prediction tool[10] (ClinRisk Ltd, Leeds, UK), although it is considering lifetime risk prediction tools for the next guideline update.[13] The original QRISK® (ClinRisk Ltd) and QRISK2 risk prediction tools have been externally validated in UK data by the original developers[14] and by independent teams,[15–17] and have been shown to have good discrimination and calibration, but QRISK®3 (ClinRisk Ltd) has not been externally validated in a UK population, which is a requirement for widespread implementation. For the prevention of osteoporotic fracture using bisphosphonates, NICE recommends using either QFracture-2012 (ClinRisk Ltd) or FRAX® (Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK).[12] The first version of QFracture-2012[17] has been externally validated in UK data by independent teams,[18] and the 2012 version has been externally validated by the original developers,[19] again finding good discrimination and calibration. In contrast, even though it is recommended by NICE, FRAX has never been externally validated to current standards[20,21] because the risk prediction algorithm is not publicly available (the external validation published by the original developers does not report discrimination in the conventional way, or calibration[22]).

Based on a model-based CEA, the NICE lipid modification guidelines recommend that clinicians offer statins to all people for whom predicted risk over 10 years is > 10%.[10] However, age is the strongest determinant of CVD risk, and a large majority of people in the UK will cross this threshold by age 65 years, irrespective of the presence of other CVD risk factors included in the model. Therefore, the guideline effectively recommends that all older people without CVD should be offered lifelong treatment with a statin. Similar issues apply to fracture risk prediction, where age dominates risk. NICE recommends risk assessment using a risk prediction tool for older people and for younger people with clinical risk factors for fracture, and concludes that bisphosphonates are cost-effective for those with a 1% risk of major osteoporotic fracture (MOF) over 10 years,[12] but without clearly specifying that this is a threshold at which clinicians should offer treatment, and the NICE aid to patient decision-making shows data only for much higher thresholds of risk.[23]

Competing mortality risk and multimorbidity

Most risk prediction tools do not account for competing mortality risk. Competing mortality risks occur when someone is at risk of death from an unrelated condition to the one being studied (e.g. death from Parkinson's disease in a study of ischaemic heart disease). Competing mortality risk is more common among people with multimorbidity than those with single conditions, and more common among older people than younger people.[24] Risk prediction models can be designed to account for competing mortality risk, but most do not. In the context of this study, QRISK3[25] and QFracture-2012[26] do not account for competing mortality risk. QRISK®-Lifetime (ClinRisk Ltd) does account for competing mortality risk,[27] as does FRAX[22,28] (but FRAX cannot be externally validated because the risk prediction algorithm is not publicly available).

Competing risk is a well-recognised problem in survival analysis.[29–33] In essence, conventional survival analysis and risk prediction tool development treats death from unrelated conditions as a censoring event equivalent to loss to follow-up for other reasons. The underlying assumption is that censored individuals have the same risk of the outcome being examined as those remaining in the study. Although this may be reasonable for ordinary loss to follow-up, this is clearly not true for people who have died. The consequence is that prediction models that do not account for competing risk in their development overestimate the risk of the outcome among those with competing risks.[29,31,32]

Studies comparing conventional models with models that are adjusted for competing risk have shown that conventional models, on average, overpredict CVD risk,[27,34–36] but the effect of competing risks has not been systematically examined in the context of fracture risk prediction (although the NICE bisphosphonate guidance[23] acknowledges that QFracture-2012 and FRAX risk predictions are difficult to compare as a result). Of note is that conventional external validation of risk prediction tools such as QRISK3 and QFracture-2012 also does not account for competing mortality risk, so the excellent observed calibration in external validation is in the context of making the same assumptions about competing mortality risk as prediction tool derivation.[16,18,19]

Therefore, the risk prediction modelling element of this project is concerned, first, with external validation of existing risk prediction tools recommended by NICE (QFracture-2012) or being considered by NICE (QRISK3), accounting for competing mortality risks and examining performance in important subgroups [objective 1, whereby examination of the subgroups of people with diabetes and chronic kidney disease (CKD) was funded by the costed extension to the original grant], and, second, with the derivation and internal validation of new risk prediction tools that account for competing mortality risk in derivation (objective 2). In addition, funded by the costed extension to the original grant, we have completed an external validation of the QRISK-Lifetime tool (objective 3).

Model-based cost-effectiveness analysis

Model-based CEAs are a key source of evidence in the development of clinical guidelines by NICE and some other guideline developers. If preventative interventions are to be offered, we need robust, population-level evidence that the technologies in question provide net benefit when compared with other possible options, including no treatment. However, the single-disease approach for creating guidelines is increasingly recognised as problematic by NICE, other guideline developers and guideline users.[37,38] Most people with any long-term condition and most people aged ≥ 65 years have multimorbidity,[4] and there is a demand for guidance that accommodates the needs of these more complex populations.[1] Failing to account for people with multimorbidity means that guidelines may be less useful, and risks recommendations (rightly or wrongly) not being adhered to. There is emerging evidence that taking account of multimorbidity will affect the total net benefit estimated for interventions, which, in turn, will influence whether or not to recommend the intervention for use in clinical practice. This evidence has indicated the need to account for important subgroups of the total patient population and the role of heterogeneity in the evidence base for different types

of patients.[39] Evidence from the 'Better Guidelines' project has shown that accounting for plausible levels of competing mortality risks associated with multimorbidity and of direct treatment disutility (DTD) (the impact on health status of taking a long-term preventative medicine irrespective of specific adverse effects of the actual drug) could also influence if, and when, overall net benefit is achieved.[2,40,41] Consequently, the methods used to structure and populate model-based CEAs need to be reconsidered to examine the impact of better accounting for multimorbidity.

Models used in CEAs do account for competing mortality risks in that they typically simulate both population age-specific total mortality and cause-specific mortality related to the condition the guideline is addressing. However, treatments that are cost-effective on average may be less cost-effective (or judged not to be cost-effective) in important subgroups, such as people with life-limiting conditions for whom population-average mortality underestimates true mortality, and therefore likely overestimates treatment benefit.[39,42] In the 'Better Guidelines' project, we explored the impact of varying competing risks of death using the NICE lipid modification cost-effectiveness model; we found that plausible increases in competing risks significantly affected expected lifetime quality-adjusted life-year (QALY) gain, and, therefore, potentially cost-effectiveness, at different baseline risk thresholds for initiating statin treatment.[2,41] However, we could not find any published data on the distribution of competing risks across the population, which meant that it was not possible to properly explore the implications of this for cost-effectiveness. Of note is that people with greater risk of CVD or fracture will typically also have greater competing risk of non-CVD or non-fracture death. This is because, for example, smoking causes both CVD and fatal respiratory disease of various kinds, and increasing age and nursing home residence are associated with both fracture risk and risk of death from many causes.

A second way in which cost-effectiveness models may be misleading is if they do not include all harms. In the 'Better Guidelines' project, we examined the impact of accounting for one type of harm that is currently ignored by existing models: DTD. We define DTD as being the collective set of individuals' strengths of preference for not taking a medicine long term, which may arise for a number of reasons. Patients are likely to value negatively the inconvenience of obtaining prescriptions from general practitioners (GPs) and collecting medicines from pharmacies; of taking medicines regularly; of having to attend for monitoring of various kinds; and of needing to modify their lifestyle to take the medicines, as is the case for bisphosphonates, for example. For some patients, taking a regular medicine or other intervention for life is an unpalatable prospect in its own right in addition to the specific hassles of being on treatment. The concept of DTD is over and above the disbenefit (i.e. harm) captured by attaching a disutility (i.e. negative impact on health status) associated with adverse drug events (ADEs) or the financial (out-of-pocket) costs for a patient. Recent studies with statins, for example, show that most or nearly all muscle aching associated with statins is a nocebo effect, as participants experience the same increase in muscle aching, compared with no tablet-taking, irrespective of whether the tablet taken contains a statin or is a placebo.[43] However, in practical terms, such individuals will experience a quality-of-life decrement if they take a statin (it is just that that decrement is not an ADE, as such). The disutility of ADEs is usually included in decision models to some extent. However, the negative impact of taking a medicine long term or for life irrespective of ADEs, especially a preventative medicine with no obvious immediate benefits, is currently ignored in model-based CEA.

In the 'Better Guidelines' project, we found that even very low plausible levels of DTD could significantly reduce, or even reverse, expected lifetime QALY gain in the context of statin treatment at the NICE treatment threshold of 10% CVD risk at 10 years, where treatment had a slowly accruing and relatively modest lifetime net benefit.[2,41] There is a small published body of literature in this field, with the cost-effectiveness of several primary preventative treatments shown to be sensitive to even small levels of DTD or treatment burden,[44–46] but there is a need to better quantify DTD because DTD values have been elicited in only a small number of studies and there is uncertainty as to their magnitude and distribution.[47,48] DTD may also vary by treatment. For example, statins to prevent CVD have to be taken daily, compared with weekly bisphosphonates to prevent fracture, but the routine for taking bisphosphonates is much more complicated (taken on an empty stomach with a significant quantity

of water and with a requirement to stay upright for at least 30 minutes and not eat or drink for 30–60 minutes after ingestion).

Therefore, this study elicits DTD values for taking lifelong statins and bisphosphonates from both general population and treated patient samples (objective 4), and uses these DTD values and data from the competing risk-adjusted prediction models to examine how expected lifetime QALY gain and cost-effectiveness of statins for primary prevention of CVD and bisphosphonates for fracture prevention vary in the presence of different levels of DTD and competing risk (objective 5).

As a subsidiary element of objective 5 (carried out as part of the costed extension to the original grant), we also sought to make the outputs of the statins model fit for present-day purposes by updating various inputs (health-related quality of life at baseline and following cardiovascular events; costs associated with interventions and cardiovascular events; type of first cardiovascular event conditional on some event having occurred). We did this because, during the development of the project, NICE announced an intention to update its guidance on CVD risk assessment and reduction, including lipid modification.[13] We did not perform similar updates for the osteoporosis model, as NICE has no similar plans to update its guidance on bisphosphonates in the foreseeable future.

Aims and objectives

The overall aim was to improve the evidence generated from risk prediction models and model-based CEAs to better inform decision-making for selecting primary prevention treatments for CVD and selecting prevention treatments for osteoporotic fracture.

The objectives were those proposed in the original grant and those included in the costed extension granted by the National Institute for Health and Care Research (NIHR):

- objective 1 – to externally validate the recommended risk prediction tools for primary prevention of CVD (QRISK3), including performance in important subgroups, and of osteoporotic fracture (QFracture-2012)
- objective 2 – to derive and internally validate new-incident CVD and osteoporotic fracture risk prediction models accounting for competing risks of death, and compare performance with existing risk prediction models
- objective 3 – to externally validate the QRISK-Lifetime risk prediction tool for primary prevention of CVD
- objective 4 – to quantify the magnitude, variation and distribution of DTD (the disutility incurred by taking a regular, long-term treatment irrespective of drug-specific side effects) in the general and statin- or bisphosphonate-treated populations
- objective 5 – to examine the effect of accounting for competing risks and DTD on clinical effectiveness and relative cost-effectiveness in the context of the use of statins and bisphosphonates for the primary prevention of CVD and osteoporotic fracture, respectively.

Project management and public involvement

The methods used for each of these objectives are described in subsequent chapters. Although all co-applicants and collaborators contributed to all aspects of the project:

- objectives 1–3 were predominantly the responsibility of the University of Dundee
- objectives 4 and 5 were predominantly the responsibility of The University of Manchester.

The literature elements of the study did not require ethics review. The prediction modelling used Clinical Practice Research Datalink (CPRD) data, and the protocol was approved by the CPRD Independent Scientific Advisory Committee (reference 16_248). The DTD elicitation study was reviewed the Health Research Authority (Integrated Research Application System project number: 220,492) and granted ethics approval (Research Ethics Committee reference 17/NW/0124).

Chapter 2 reports the external validation of QRISK3, including performance in important subgroups, and the derivation and internal validation of a new competing mortality risk model (CRISK) (objectives 1 and 2 for CVD risk prediction). *Chapter 3* reports the external validation of QRISK-Lifetime (objective 3).[49] *Chapter 4* reports the external validation of QFracture-2012, and the derivation and internal validation of a new CRISK (i.e. CFracture) (objectives 1 and 2 for fracture risk prediction).[50,51] *Chapter 5* reports the DTD elicitation (objective 4). For statins for primary prevention of CVD and bisphosphonates for prevention of fracture, *Chapters 6* and *7*, respectively, report the new model-based CEAs accounting for competing mortality risk more accurately and accounting for DTD (objective 5). *Chapter 8* summarises the findings and their implications.

Patient and public involvement

The original research proposal was informed by qualitative analysis of patient data from eight focus groups with 48 participants and nine individual interviews about prescribing and prescribing decision-making that we did as part of our Data-driven Quality Improvement in Primary care (DQIP) prescribing safety improvement programme, which finished at the end of 2014.[52] We also carried out a group discussion with eight members of an NHS Patient and Public Participation Group, and our two public partners contributed to the development of the proposal through discussion and through their membership of our previous NIHR-funded 'Better Guidelines' project reference group.[2] Unsurprisingly, across these groups, there was strong support for the idea that treatment decisions for individual conditions should take account of other conditions, other treatments and the context of the individual as a whole person, and for work examining whether such accounting could improve the quality of evidence that underpinned treatment decisions. This was significantly driven by a general perception that the number of drugs people were taking regularly was increasing, and some unease about whether the benefits of this always outweighed the harms. The conceptualisation of DTD and its existence was informed by input from patient expert members of the advisory group for the 'Better Guidelines' project. During the conduct of this project, two patient experts took active roles in the project advisory group: Alison Allen and Graham Bell. Both contributed to the development of the grant (because they were both involved in the prior project too) and were in the study advisory group, and, most specifically, contributed to the development of the DTD elicitation questionnaire, providing extensive comments on the survey design. We were sadly informed that Graham Bell passed away in late 2020, and we have been unable to re-establish contact with Alison Allen. Therefore, we have not been able to ask our patient experts for their input on the results of this project.

Chapter 2 Cardiovascular disease risk prediction: external validation of QRISK3 and derivation and internal validation of a new competing risk model (CRISK)

Background

Although the age-specific incidence of CVD has fallen steadily in most developed countries for several decades, ageing populations mean that CVD remains a major cause of morbidity and mortality worldwide. UK guidelines for the primary prevention of CVD recommend that clinicians use a risk prediction tool to target treatment with statins at people whose predicted risk exceeds a specified threshold. The recommended threshold has been progressively reduced, with NICE changing its recommendation for England and Wales from a 10-year CVD risk of > 20% to > 10% in 2014.[10] US guidelines recommend a 7.5% threshold, although the included events are not identical.[53] Risk thresholds have been reduced because of increasing evidence of statin effectiveness for primary prevention, and the increasing cost-effectiveness of statins at lower thresholds of baseline risk because statin prices have fallen as they come off patent.

Such risk-stratified guideline recommendations are reliant on the availability of prediction tools for CVD risk. The risk prediction tools recommended in different countries and guidelines vary, reflecting variation in CVD risk factors and incidence, and reflecting that locally derived and validated tools are more likely to be appropriate to local contexts. NICE recommends the use of QRISK2 to predict CVD risk.[10] QRISK2 has been externally validated in UK primary-care data sets, and has excellent discrimination and calibration at whole-population level when evaluated on its own terms (ignoring competing mortality risk).[16] QRISK3 is a new version of the same tool that includes additional morbidities in prediction. QRISK3 has been derived and internally validated using the same methodology as for QRISK2,[25] and in internal validation has excellent model discrimination in the overall population and among younger people, but only good discrimination among older people (defined as those aged ≥ 60 years).[25] External validation is required before recommending any prediction tool for routine use.[20,21,54,55]

However, as with its predecessors, QRISK3 does not account for competing mortality risk in its derivation. The effects of competing mortality risk are obvious in the extreme: taking a statin is clearly futile for someone receiving end-of-life care for terminal cancer. However, across a 10-year prediction time horizon, less dramatic levels of competing mortality risk can lead to systematic and clinically significant overprediction of CVD risk among people at higher risk of dying from another cause, which will particularly apply to older people and those with multimorbidity.[34,35]

In addition, because age dominates CVD risk, a risk prediction tool that covers a wide range of ages (25–84 years in the case of QRISK3) will always have good discrimination at overall population level. However, discrimination and calibration in subgroups may be poor. This is observed in reported discrimination for QRISK3 in internal validation, where, for example, discrimination is better among younger than older people, and is better among those with type 1 diabetes than those with type 2 diabetes (see the supplementary appendix of the derivation and internal validation paper[25]), although calibration in different groups is not reported.

In terms of NICE's surveillance review of the lipid modification guideline, two particular subgroups of interest are people with type 1 diabetes and people with CKD.[13] There is some evidence that models

derived in people with diabetes have somewhat better discrimination in diabetic populations than models derived in the general population, although the evidence is primarily for people with type 2 diabetes.[56] Discrimination of CVD risk prediction models in people with type 2 diabetes is generally poor,[57] particularly in older adults.[58] QRISK3 does include a type 1 diabetes variable and so, in principle, provides a type 1 diabetes-specific prediction in a model derived from a whole population,[25] and the Steno Type 1 Risk Engine (Steno Diabetes Center, Copenhagen, Denmark) provides an alternative derived from a population of people with type 1 diabetes;[59] however, at the time this study was carried out, neither tool had been externally validated (an external validation[60] published after we completed this element of the study is discussed in *Summary*). In people with CKD, CVD risk prediction tools that do not account for CKD substantially underpredict CVD risk,[61–63] although adding a detailed indicator of estimated glomerular filtration rate (eGFR) and albuminuria to models calibrated to the CKD population leads to only small improvements in discrimination.[64]

This study, therefore, externally evaluates the performance of QRISK3 both in its own terms (ignoring competing mortality risk) and accounting for competing risk, and examines model performance in subgroups of the population defined by age and by levels of comorbidity [a modified Charlson Comorbidity Index[65] (mCCI)], for whom competing mortality risk is likely to vary, and in people with type 1 diabetes and CKD.

We then derive a new CVD prediction model based on QRISK3 that accounts for competing mortality risks (i.e. the CRISK), internally validate the model in the same data set and examine reclassification from using CRISK compared with using QRISK3 to identify people with predicted 10-year CVD risk of > 10%.

This chapter reports methods and findings for CVD risk prediction models in relation to objectives 1 and 2, as follows:

1. To externally validate the recommended risk prediction tools for primary prevention of CVD (QRISK3), including performance in important subgroups, and for osteoporotic fracture (QFracture-2012).
2. To derive and internally validate new-incident CVD (and osteoporotic fracture) risk prediction models, accounting for competing risks of death, and compare performance with existing risk prediction models.

Methods

Data sources

Data used in this study were taken from CPRD GOLD,[66] which derives data from general practices using INPS Vision electronic health records and is distinct from the derivation data set, which is derived from practices using the EMIS system. Identical to QRISK3 derivation and internal validation, patients were eligible for inclusion if they:

- were permanently registered with a general practice, contributing up-to-standard data for at least 1 year and with consent to link GP data to hospital discharge (Hospital Episodes Statistics Admitted Patient Care) and mortality [Office for National Statistics (ONS) mortality registration] data
- were aged ≥ 25 years and < 85 years
- had no prior history of any CVD
- had no prior history of statin prescription.

Cohort entry was defined as the latest date of an individual's date of registration plus 1 year, the individual's 25th birthday or 1 January 2004. Cohort exit was defined as the earliest of:

- the first non-fatal or fatal cardiovascular event
- receipt of a statin prescription

- deregistration from their participating general practice
- date of last data collection from their participating general practice
- end-of-study follow-up on 31 March 2016.

Of note, the QRISK3 derivation and internal validation did not censor on statin prescription, but we chose to, as the primary purpose of the tool is to inform decisions on statin initiation.

Sample size

The sample size is fixed by the size of the CPRD GOLD data set. Therefore, no formal power calculation was carried out, as it could not alter study design and the available sample size was considered sufficient for the purpose.[54]

Outcome definition

The outcome was the first CVD event experienced by an individual, defined as the earliest GP, hospital or mortality record of non-fatal coronary heart disease, ischaemic stroke or transient ischaemic attack (TIA). Outcomes were defined using Read codes (for GP data) and *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10) codes (for hospital discharge and mortality data). ICD-10 codes are those listed in the published QRISK3 derivation paper;[25] however, there are no published Read codesets available. We, therefore, derived our own Read codeset, and this and the ICD-10 codes are listed in appendices to the published paper[67] reporting our external validation of QRISK3.

Other variable definitions

At the time the analysis was done, there were no published Read codesets for other variables included in the QRISK3 model, which we defined using Read codes in GP data which we created for this study and values [e.g. systolic blood pressure (SBP), cholesterol] in GP data (listed in our published paper).[67] There were several data-handling variations compared with the original QRISK3 derivation:

- We chose a later cohort entry date (1 January 2004 vs. 1 January 1998).
- Where no cholesterol value was available at baseline, then QRISK3 allowed cholesterol values after the cohort entry date to be used provided that they were before any CVD event. In contrast, we used values from before the cohort entry date only to avoid using future information in prediction.
- CPRD makes only group Townsend deprivation scores available as vigintile (equal 20th) of Townsend score. Therefore, we estimated the median Townsend score of national vigintiles and used that in prediction.

In addition, we calculated a mCCI based on Read codes in the GP data, using a published codeset.[65] The mCCI was modified in that the original Charlson Comorbidity Index (CCI) includes several CVDs that are, by definition, excluded at baseline in this study because participants are CVD free at baseline. The mCCI was not used in prediction but was used to examine discrimination and calibration in subgroup analysis (categorised as 0, 1, 2 and ≥ 3), along with age group (categorised as 25–44 years, 45–64 years, 65–74 years and 75–84 years).

Missing data

Missing data handling and the proportion of each variable with missing data are shown in *Appendix 1*, *Table 24*. As with QRISK3 derivation, patients were excluded if the Townsend deprivation score was missing, patients with missing data on ethnicity were assumed to be white and patients with no record of a condition were assumed not to have the condition. For continuous variables [i.e. body mass index (BMI), total cholesterol : high-density lipoprotein ratio (TC : HDL), SBP, SBP variability] and for smoking status, multivariate imputation via chained equations[68] was used to generate five imputed data sets. Analyses of these imputed data sets were combined using Rubin's rules to account for the uncertainty association with imputation.[69]

Analytical methods: external validation

The published QRISK3 2017 prediction model was implemented (under GNU Lesser General Public Licence v3), and the predicted 10-year risk of experiencing a CVD event was calculated for each patient without recalibration of baseline risk. Model performance was evaluated by examining discrimination and calibration.

Discrimination evaluates how well the risk score differentiates between patients who experience a CVD event (or more generally, the event of interest) during the study and patients who do not. We primarily examined discrimination using the truncated version of Harrell's *c*-statistic to include only pairs where the earliest survival time was no later than 10 years after entry. A *c*-statistic of 0.5 indicates that the risk score performs no better than chance, whereas a *c*-statistic of 1 indicates perfect discrimination. Evaluating how good discrimination is for values between 0.5 and 1 is arbitrary and involves judgement. We considered *c*-statistic values of 0.5–0.599 poor, values of 0.6–0.699 moderate, values of 0.7–0.799 good and values > 0.8 excellent.

Two additional measures of discrimination were calculated. First, we calculated Royston and Sauerbrei's D-statistic (based on the separation in event-free survival between patients with predicted risk scores above and below the median, where higher values indicate greater discrimination and a difference of ≥ 0.1 is suggested as indicating a meaningful difference in discrimination).[70] Second, we calculated a related R^2-statistic designed for estimating explained variation in censored survival data.[71]

Models may have good discrimination but imperfectly predict risk, for example by systematically overpredicting or underpredicting. Examination of calibration is, therefore, important, particularly where predicted risk is used to determine offers of treatment, as it is for primary prevention of CVD.[10] Calibration refers to how closely the predicted and observed probabilities agree at group level, and for this purpose participants were grouped into 10 equal-sized groups (deciles) of predicted risk. Calibration of the risk score predictions was assessed by plotting observed proportions against predicted probabilities. For both men and women separately, plots were generated for all patients and for prespecified subgroups of age, mCCI, diabetes type and CKD, based on summary statistics pooled across the imputed data sets. Subgroups were defined to ensure that there were enough events in each subgroup to ensure stable estimates of observed risk (and for diabetes and CKD, analysis was, therefore, in the whole subgroup without further stratification for age group or mCCI). CKD was defined in two ways: (1) only using Read codes,[67] as per QRISK3 derivation[25] and (2) using the same set of Read codes or the last recorded eGFR or eGFR based on last recorded serum creatinine, where an eGFR < 60 ml per minute defined CKD.

The following summary statistics and their standard errors (SEs) were obtained by decile of predicted risk score and for each imputed data set, in turn: non-parametric measures of observed risk or proportions of patients with a CVD event, the Kaplan–Meier estimator (the conventional measure ignoring competing risks), the Aalen–Johansen estimator (an extension to allow for competing events, non-CVD death in this case)[16] and the mean predicted risk score. All models were fitted in R 4.0.0 (The R Foundation for Statistical Computing, Vienna, Austria) and Stata® 11.2 (StataCorp LP, College Station, TX, USA).

Analytical methods: competing risk model derivation and internal validation

Competing risk model derivation and internal validation was carried out in the same data set as QRISK3 external validation. For this purpose, participants were randomly allocated to distinct derivation and test data sets in a 2 : 1 ratio, with allocation balanced in terms of age and final event status. The derivation data set was used to derive CRISK, that is a Fine–Gray model to predict the 10-year risk of experiencing a CVD event, accounting for the competing risk of non-CVD death. Separate models were estimated for men and women. Reflecting the overall aim of the project, where we wished to explicitly compare prediction in models accounting for competing risk compared with ignoring competing risk, we included all of the same main effects (i.e. predictors) and age interactions as QRISK3, modified as follows. First,

we accounted for non-CVD death as a second (competing) outcome using the Fine–Gray model, and we re-estimated fractional polynomial terms for continuous variables, including in QRISK3, selecting terms based on those performing best (as measured by the *c*-statistic) in balanced 10-fold cross-validation and showing consistency of model fit [i.e. Akaike information criterion (AIC)] across folds of the derivation data set (this model is called CRISK). Second, as QRISK3 predictors are focused on CVD events, we derived a further model [i.e. the competing mortality risk model with Charlson Comorbidity Index (CRISK-CCI)], which additionally included the mCCI score in the model (categorised as 0, 1, 2, ≥ 3), as CCI is a well-validated predictor of total mortality.[12] Fine–Gray models allow the cumulative incidence function or probability of a CVD event occurring over time to be directly predicted; however, the subdistribution hazard ratios (HRs) in the Fine–Gray models do not have a straightforward interpretation, as they describe the direction but not the magnitude of the effect of predictors on the cumulative incidence function. The use of fractional polynomials and the inclusion of complex interactions with age further complicate direct interpretation of model coefficients. Model coefficients are, therefore, not straightforwardly interpretable, but the derived model is provided in *Appendix 1*, *Tables 25* and *26*, to allow replication.

The performance of all three models (i.e. CRISK, CRISK-CCI and QRISK3) was evaluated in the independent validation data set by examining discrimination and calibration, as described above. R 4.0.0 was used for all analyses.

Results 1: external validation of QRISK3 in the whole population

The external validation data set had 1,648,746 women aged 25–84 years with linkage to Hospital Episode Statistics (HES) and ONS. Of these women, 164,129 (10.0%) were excluded because of missing deprivation score (0.2%), prior CVD (4.7%) or prior statin prescribing (5.1%). The external validation data set had 1,621,535 men aged 25–84 years with linkage HES and ONS. Of these men, 201,359 (12.4%) were excluded because of missing deprivation score (0.2%), prior CVD (6.9%) or prior statin prescribing (5.3%). Therefore, analysis used data for 1,484,597 women and 1,420,176 men.

The baseline characteristics of participants compared with the QRISK3 internal validation cohort[25] are shown in *Appendix 1*, *Table 27*. The two cohorts were similar, although there was a higher prevalence of treated hypertension in this study, and a lower recorded prevalence of family history of premature CVD. *Appendix 1*, *Table 24*, shows that ethnicity data were less frequently missing in this study, but that TC : HDL, SBP variability and smoking status were more commonly missing (which may reflect the use of data after study entry date in QRISK3 derivation).

In women, during 8,594,620 years of follow-up, there were 42,451 incident cases of CVD observed {4.94 [95% confidence interval (CI) 4.89 to 4.99] per 1000 person-years}. In men, during 7,896,704 years of follow-up, there were 53,066 incident cases [6.72 (95% CI 6.66 to 6.78) per 1000 person-years]. Incidence progressively rose with age, from 0.3 cases per 1000 person-years in both men and women aged 25–29 years, to 44.1 cases in women aged 80–84 years and to 52.6 cases in men aged 80–84 years. CVD incidence was moderately lower than that observed in QRISK3 derivation (see *Appendix 1*, *Table 28*).[4]

In the whole population, discrimination was excellent in both women (Harrell's *c*-statistic 0.865, 95% CI 0.861 to 0.868) and men (Harrell's *c*-statistic 0.834, 95% CI 0.831 to 0.837), and very similar to QRISK3 internal validation (women, Harrell's *c*-statistic 0.880; men, Harrell's *c*-statistic 0.858)[25] (*Table 1*). The D-statistic was 2.43 in women (similar to the internal validation study's D-statistic of 2.49) and 2.10 in men (somewhat lower than the internal validation study's D-statistic of 2.26). Explained variation (R^2) was 58.5% in women and 51.3% in men, compared with 59.6% and 55.0%, respectively, in the internal validation study. In all strata of age group, discrimination was worse in both men and women, varying from good in younger people (age 25–44 years Harrell's *c*-statistic: women, 0.865; men, 0.757) to poor

TABLE 1 Discrimination of QRISK3 in the whole population and stratified by age group and mCCI

	Women			Men		
Population subgroups	**Harrell's *c*-statistic (95% CI)**	**D-statistic (95% CI)**	**R^2-statistic (95% CI)**	**Harrell's *c*-statistic (95% CI)**	**D-statistic (95% CI)**	**R^2-statistic (95% CI)**
All patients	0.865 (0.861 to 0.868)	2.43 (2.41 to 2.45)	58.5 (58.1 to 58.8)	0.834 (0.831 to 0.837)	2.10 (2.08 to 2.12)	51.3 (50.8 to 51.7)
Age group (years)						
25–44	0.758 (0.747 to 0.769)	1.69 (1.63 to 1.76)	40.7 (38.8 to 42.5)	0.757 (0.749 to 0.764)	1.57 (1.52 to 1.61)	36.9 (35.6 to 38.2)
45–64	0.707 (0.702 to 0.713)	1.25 (1.22 to 1.28)	27.2 (26.1 to 28.3)	0.681 (0.677 to 0.685)	1.04 (1.02 to 1.07)	20.6 (19.8 to 21.4)
65–74	0.641 (0.635 to 0.647)	0.82 (0.77 to 0.86)	13.7 (12.4 to 15.1)	0.612 (0.606 to 0.617)	0.63 (0.59 to 0.66)	8.6 (7.7 to 9.5)
75–84	0.611 (0.605 to 0.616)	0.61 (0.56 to 0.66)	8.1 (6.9 to 9.3)	0.585 (0.579 to 0.591)	0.46 (0.42 to 0.51)	4.9 (4.1 to 5.8)
mCCI						
0	0.863 (0.859 to 0.867)	2.40 (2.38 to 2.43)	57.9 (57.4 to 58.4)	0.827 (0.824 to 0.831)	2.02 (2.00 to 2.04)	49.4 (48.9 to 49.8)
1	0.846 (0.840 to 0.852)	2.20 (2.17 to 2.24)	53.6 (52.8 to 54.4)	0.829 (0.823 to 0.835)	2.00 (1.96 to 2.03)	48.7 (47.8 to 49.6)
2	0.789 (0.778 to 0.799)	1.73 (1.67 to 1.78)	41.6 (39.9 to 43.2)	0.728 (0.717 to 0.739)	1.28 (1.22 to 1.34)	28.1 (26.2 to 29.9)
≥ 3	0.744 (0.728 to 0.760)	1.40 (1.32 to 1.48)	31.8 (29.2 to 34.4)	0.695 (0.678 to 0.712)	1.13 (1.04 to 1.21)	23.2 (20.5 to 26.0)

to moderate in older people (age 75–84 years Harrell's *c*-statistic: women, 0.611; men, 0.585), with low levels of explained variation in older people (age 75–84 years R^2: women, 8.1%; men, 4.9%). Stratified by mCCI, discrimination was excellent in people with low comorbidity, but progressively less good in people with higher comorbidity, but with less change than for age group (mCCI ≥ 3 Harrell's *c*-statistic: women, 0.744; men, 0.695).

Ignoring competing mortality risk in the estimation of observed risk (*Figures 1* and *2*, parts a, c and e), calibration in the whole population was very good, with only minor overprediction in people at higher predicted risk (see *Figures 1* and *2*, part a). Stratified by age, overprediction was larger in older people (see *Figures 1* and *2*, part b). Stratified by mCCI, there was some overprediction in people with no baseline comorbidity, but underprediction in those with comorbidity (see *Figures 1* and *2*, part c). Accounting for competing mortality risk in the estimation of observed risk (see *Figures 1* and *2*, parts b, d and f), overprediction was larger in the whole population and in all age groups apart from the youngest (i.e. people aged 25–44 years) (see *Figures 1* and *2*, parts d and e). Stratified by mCCI, underprediction was still observed in people with higher comorbidity at lower levels of predicted risk, but there was large overprediction in people with higher comorbidity at higher levels of predicted risk (see *Figures 1* and *2*, part f).

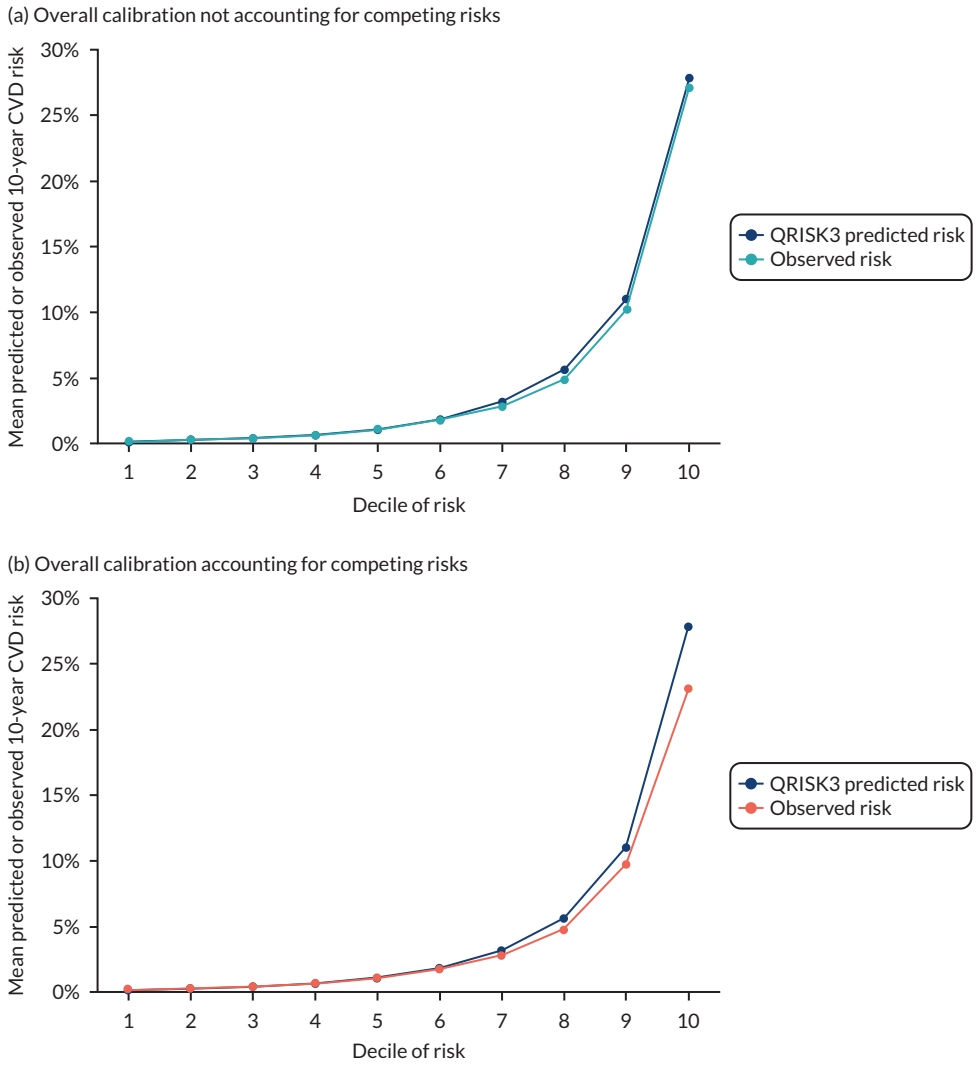


FIGURE 1 Calibration in women without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. (*continued*)

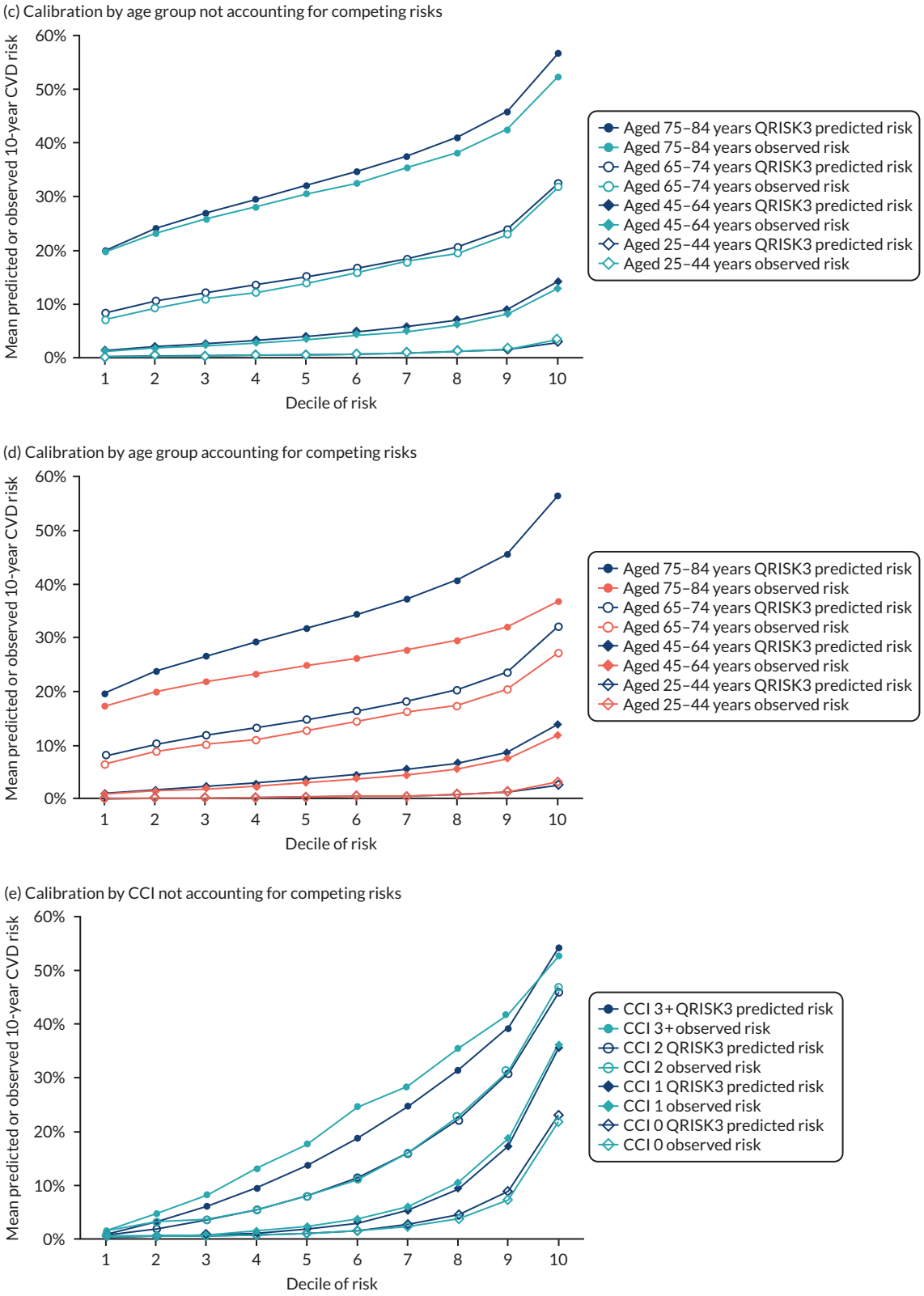


FIGURE 1 Calibration in women without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. (*continued*)

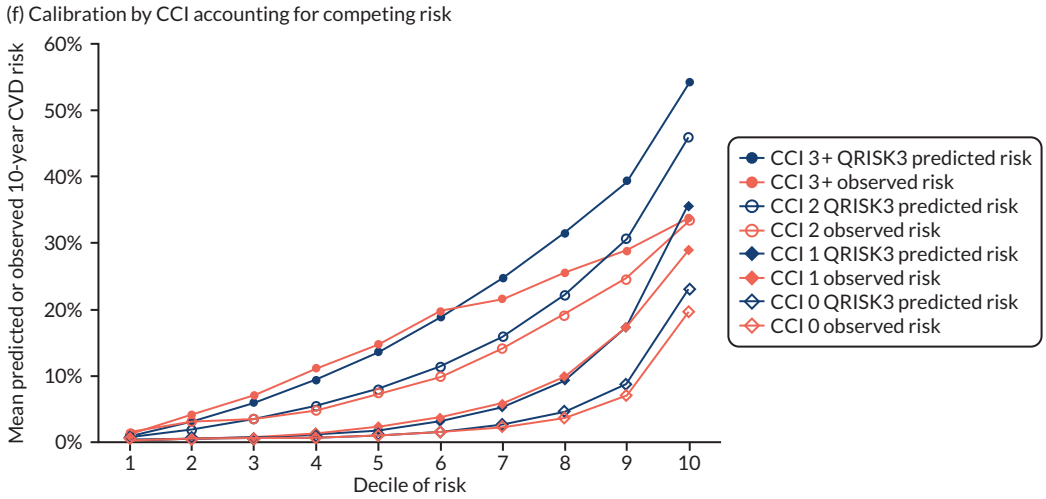


FIGURE 1 Calibration in women without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk.

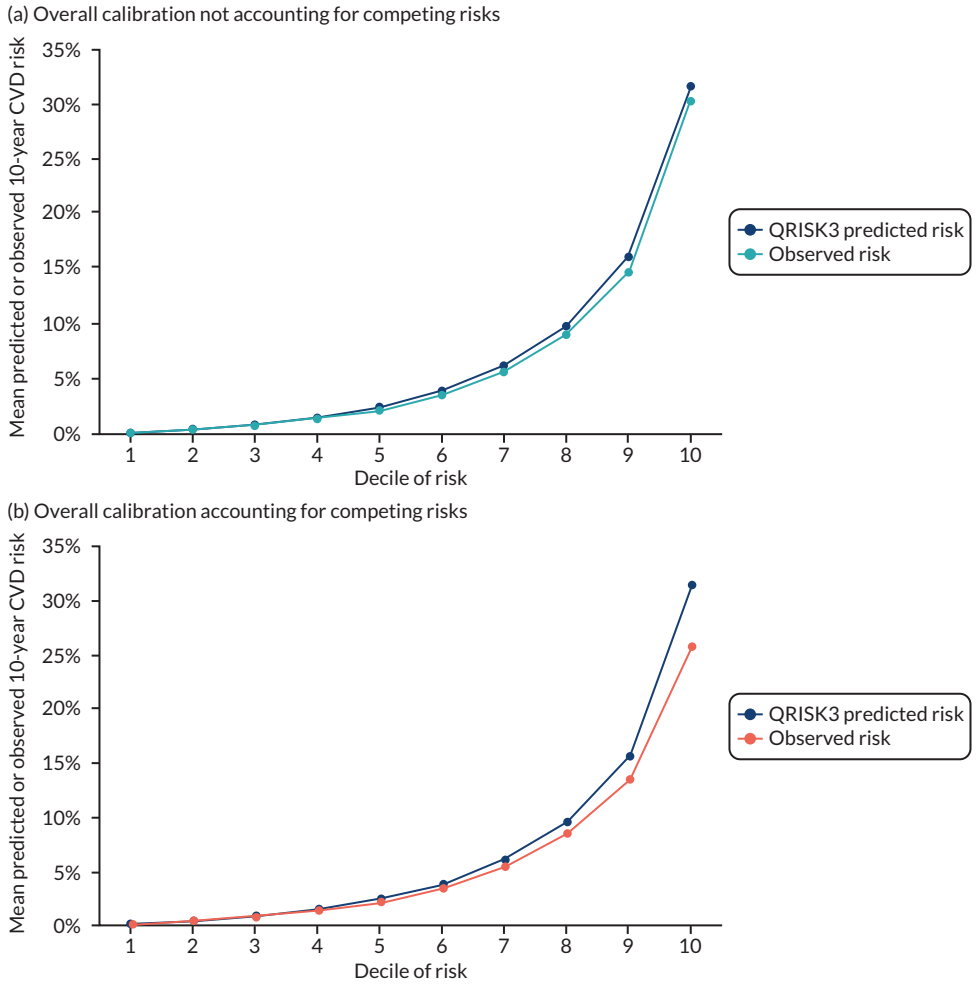


FIGURE 2 Calibration in men without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. (*continued*)

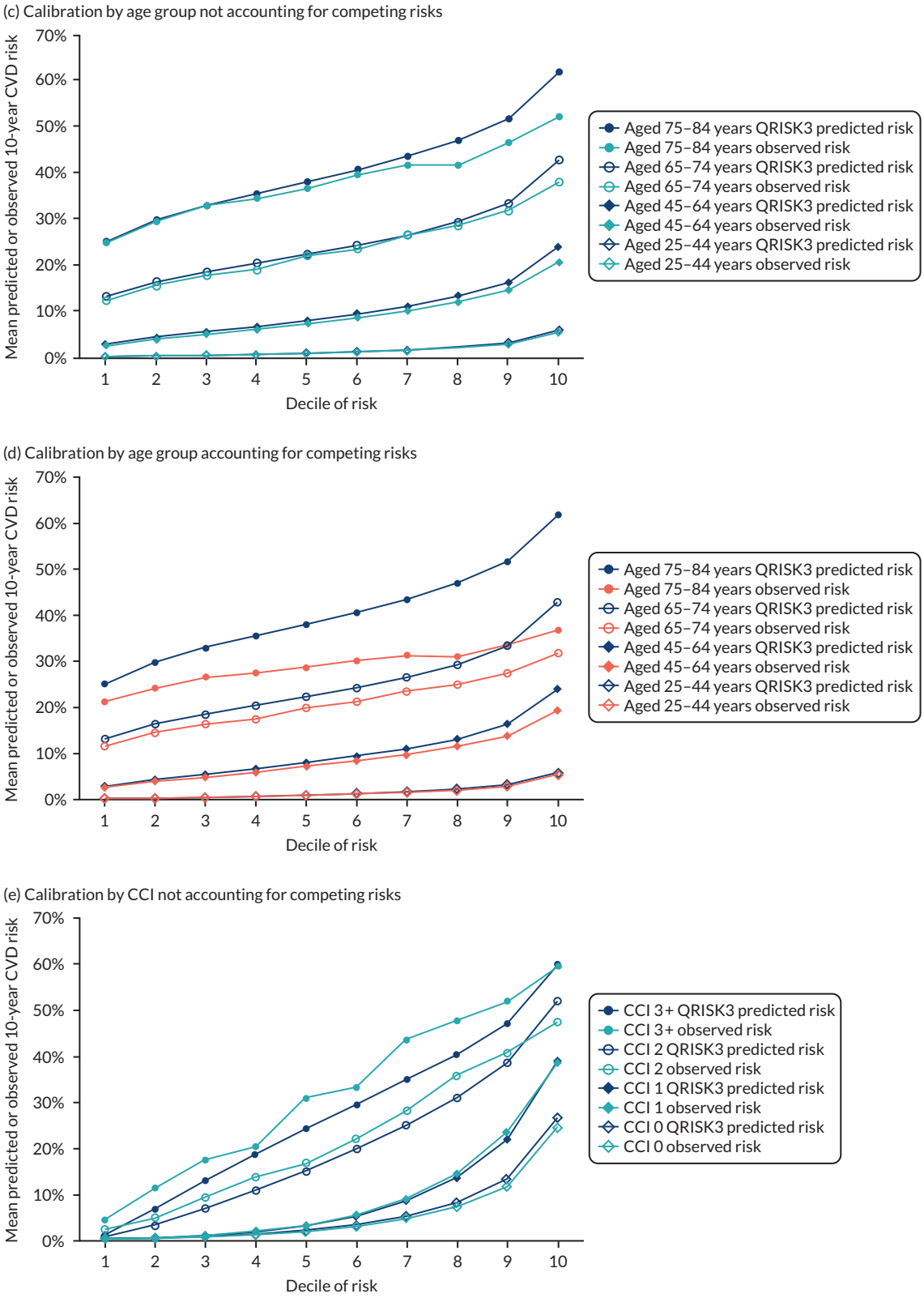


FIGURE 2 Calibration in men without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. (*continued*)

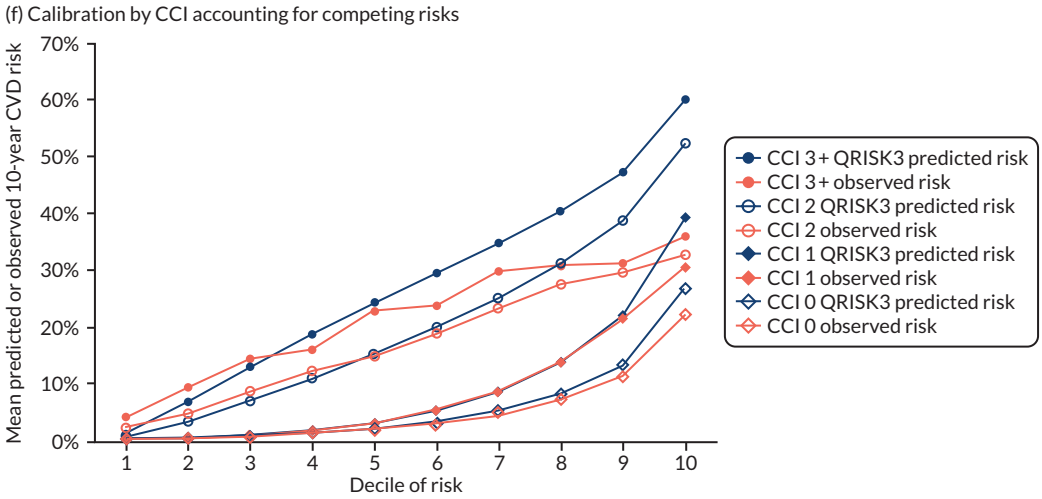


FIGURE 2 Calibration in men without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk.

Results 2: external validation of QRISK3 in people with diabetes

Type 1 diabetes

There were 6025 women with type 1 diabetes potentially eligible for inclusion, of whom 646 (10.7%) and 1627 (27.0%) were excluded because of prior CVD or prior statin prescribing for primary prevention, respectively. There were 8260 men with type 1 diabetes potentially eligible for inclusion, of whom 953 (11.5%) and 2464 (40.9%) were excluded because of prior CVD or prior statin prescribing for primary prevention, respectively. Therefore, 3752 women (62.3% of potentially eligible women with type 1 diabetes) and 4843 men (48.6% of potentially eligible men with type 1 diabetes) were included in analysis of type 1 diabetes.

During follow-up of the type 1 diabetes cohort, there were 108 CVD events in 13,098 person-years' follow-up in women [8.25 (95% CI 6.83 to 9.94) events per 1000 person-years] and 172 CVD events in 15,824 person-years' follow-up in men [10.90 (95% CI 9.40 to 12.60) events per 1000 person-years].

Discrimination in people with type 1 diabetes was excellent [Harrell's *c*-statistic: women, 0.830 [95% CI 0.768 to 0.891; men, 0.853 (95% CI 0.803 to 0.902)] and explained variance in the model was 51.6% in women and 48.0% in men (see *Appendix 1*, *Table 29*).

Ignoring competing risks (see *Appendix 1*, *Figure 28*, parts a and c), calibration in women with type 1 diabetes was good (allowing for small number of events and, therefore, a relatively noisy plot), but there was some overprediction in men at higher predicted risk. Accounting for competing risks (see *Appendix 1*, *Figure 28*, parts b and d), there was overprediction in women at higher predicted risk and greater overprediction in men at higher predicted risk.

Type 2 diabetes

There were 53,284 women with type 2 diabetes potentially eligible for inclusion, of whom 12,068 (22.6%) and 24,194 (45.4%) were excluded because of prior CVD or prior statin prescribing for primary prevention, respectively. There were 68,236 men with type 2 diabetes potentially eligible for inclusion, of whom 19,777 (28.9%) and 27,382 (40.1%) were excluded because of prior statin prescribing for primary prevention, respectively. Therefore, 24,194 women (i.e. 31.9% of the potentially eligible women

with type 2 diabetes) and 21,077 men (i.e. 30.9% of the potentially eligible men with type 2 diabetes) were, therefore, included in analysis of type 2 diabetes.

During follow-up of the type 2 diabetes cohort, there were 1167 CVD events in 44,678 person-years' follow-up in women [26.12 (95% CI 24.68 to 27.64) events per 1000 person-years] and 1682 CVD events in 57,160 person-years' follow-up in men [29.40 (95% CI 28.10 to 30.80) events per 1000 person-years].

Discrimination in people with type 2 diabetes was moderate to good [Harrell's *c*-statistic: women, 0.741 (95% CI 0.722 to 0.760); men, 0.695 (95% CI 0.679 to 0.712)] and explained variance in the model was lower than for type 1 diabetes (i.e. 29.2% in women and 22.0% in men) (see *Appendix 1*, *Table 29*).

Ignoring competing risks (see *Appendix 1*, *Figure 29*, parts a and c), calibration in women with type 2 diabetes was good, but there was some overprediction in men at the highest predicted risk. Accounting for competing risks (see *Appendix 1*, *Figure 29*, parts b and d), there was progressively increasing overprediction in women with moderate to high predicted risk and in men in all but the lowest deciles of predicted.

Results 3: external validation of QRISK3 in people with chronic kidney disease

Chronic kidney disease defined by Read code alone

There were 16,048 women with CKD defined by Read code alone potentially eligible for inclusion, of whom 4223 (26.3%) and 4897 (30.5%) were excluded because of prior CVD or prior statin prescribing for primary prevention, respectively. There were 15,784 men with CKD defined by Read code alone potentially eligible for inclusion, of whom 5645 (35.7%) and 3850 (24.4%) were excluded because of prior CVD or prior statin prescribing for primary prevention, respectively. Therefore, 6918 women (i.e. 43.1% of the potentially eligible women with CKD defined by Read code alone) and 5659 men (i.e. 35.9% of the potentially eligible men with CKD defined by Read code alone) were, therefore, included in analysis of CKD defined by Read code alone. The mean age of women was 63.0 years and mean age of men was 59.2 years.

During follow-up of the CKD defined by Read code alone cohort, there were 541 CVD events in 25,544 person-years' follow-up in women [21.18 (95% CI 19.48 to 23.02) events per 1000 person-years] and 569 CVD events in 21,459 person-years' follow-up in men [26.50 (95% CI 24.40 to 28.80) events per 1000 person-years].

Discrimination in people with CKD defined by Read code alone was good [Harrell's *c*-statistic: women, 0.755 (95% CI 0.728 to 0.782); men, 0.734 (95% CI 0.708 to 0.760)] and explained variance in the model was 34.2% in women and 29.7% in men (see *Table 30*).

Ignoring competing risks (see *Appendix 1*, *Figure 30*, parts a and c), calibration in women with CKD defined by Read code alone was reasonable (allowing for small number of events and, therefore, a relatively noisy plot) and good for men (with some underprediction for both at higher predicted risk). Accounting for competing risks (see *Appendix 1*, *Figure 30*, parts b and d), there was overprediction in women at moderate and higher predicted risk and overprediction in men at higher predicted risk.

Chronic kidney disease defined by Read code and estimated glomerular filtration rate

Laboratory values were extracted for only people included in the CVD study cohort and so it is not possible to calculate the proportions excluded because of prior CVD or prior statin prescribing. There were 71,094 women and 33,699 men with CKD defined by Read code or eGFR included in analysis, with an older mean age than the cohort with CKD defined by Read code alone (mean age: women, 70.1 years; men, 69.1 years).

During follow-up of the CKD defined by Read code or eGFR cohort, there were 8877 CVD events in 348,982 person-years' follow-up in women [25.44 (95% CI 24.92 to 25.96) events per 1000 person-years] and 5273 CVD events in 146,730 person-years' follow-up in men [35.90 (95% CI 35.00 to 36.90) events per 1000 person-years].

Discrimination in people with CKD defined by Read code or eGFR was somewhat worse than for people with CKD defined by Read code alone. Discrimination was moderate to good [Harrell's *c*-statistic: women, 0.705 (95% CI 0.699 to 0.712); men, 0.671 (95% CI 0.663 to 0.680)] and explained variance in the model was somewhat lower than for CKD defined by Read code alone (i.e. 24.9% in women and 17.4% in men) (see *Table 30*).

Ignoring competing risks (see *Appendix 1*, *Figure 31*, parts a and c), calibration in women with CKD defined by Read code or eGFR was excellent, but there was some underprediction in men. Accounting for competing risks (see *Appendix 1*, *Figure 31*, parts b and d), there was progressively increasing overprediction in women and men with moderate to high predicted risk.

Results 4: derivation and internal validation of CRISK

There were 989,732 women and 946,784 men aged 25–84 years in the derivation cohort, and 494,865 women and 473,392 men in the validation cohort, with similar distribution of baseline characteristics in each. There were 14,150 incident CVD events in 2,865,660 years of follow-up in women [4.9 (95% CI 4.89 to 4.99) events per 1000 person-years] and 17,689 incident CVD events in 2,632,804 years of follow-up in men [6.7 (95% CI 6.66 to 6.78) events per 1000 person-years].

Two new models were created: (1) CRISK that is a near replication of QRISK3, which accounts for competing risk and (2) CRISK-CCI, which additionally includes the mCCI as a predictor of competing mortality.

In the whole population, discrimination of CRISK and CRISK-CCI was excellent in women and very similar to QRISK3 (CRISK Harrell's *c*-statistic: women, 0.863; men, 0.833; CRISK-CCI Harrell's *c*-statistic: women, 0.864; men, 0.819) (*Table 2*). For both new models, discrimination showed similar patterns to QRISK3 in terms of being worse in all age groups (and progressively worse with increasing age) and, to a lesser extent, worse with increasing comorbidity measured by the mCCI (see *Table 2*).

In terms of calibration (evaluated using only the Aalen–Johansen estimator, which accounts for competing mortality risk in estimated observed risk), QRISK3 overpredicted in both men and women in the whole population, with progressively worse overprediction at higher predicted risk (see *Results 1: external validation of QRISK3 in the whole population*).

In the whole population of women, there was some overprediction with CRISK at higher levels of predicted risk, but CRISK was better calibrated than QRISK3. Calibration in women with CRISK-CCI was excellent (*Figure 3*). In younger women, there was some underprediction with all three prediction tools, which were similar, although CRISK was the best calibrated (*Figure 4*). QRISK3 and CRISK both showed overprediction in middle-aged and older women. CRISK-CCI was well calibrated in women aged 45–64 years and 65–74 years and had some overprediction at higher risk in women aged 75–84 years (but was the best calibrated model). In all CCI categories, there was some overprediction with each model at higher levels of predicted risk, which was greatest with QRISK3 and least with CRISK-CCI, although calibration of all models was broadly the same for mCCI ≥ 3 (*Figure 5*).

In the whole population of men, calibration using CRISK-CCI was better than calibration using CRISK, which showed some underprediction, whereas QRISK3 somewhat overpredicted CVD risk (see *Figure 3*). In younger men aged 25–44 years, there was some underprediction with CRISK and QRISK3, but calibration with CRISK-CCI was very good (see *Figure 4*). In middle-aged and older men, QRISK3

TABLE 2 Discrimination of CRISK-CCI, CRISK and QRISK3 for men and women in the validation cohort

Patient group	Harrell's *c*-statistic (95% CI)					
	Women			Men		
	CRISK-CCI	CRISK	QRISK3	CRISK-CCI	CRISK	QRISK3
All patients	0.864 (0.859 to 0.869)	0.863 (0.858 to 0.869)	0.863 (0.858 to 0.868)	0.819 (0.815 to 0.824)	0.833 (0.828 to 0.837)	0.832 (0.827 to 0.836)
Age group (years)						
25–44	0.763 (0.745 to 0.781)	0.761 (0.743 to 0.779)	0.765 (0.747 to 0.783)	0.733 (0.720 to 0.746)	0.744 (0.731 to 0.757)	0.740 (0.727 to 0.753)
45–64	0.713 (0.703 to 0.722)	0.710 (0.701 to 0.720)	0.708 (0.698 to 0.717)	0.661 (0.654 to 0.668)	0.683 (0.676 to 0.690)	0.679 (0.672 to 0.686)
65–74	0.647 (0.637 to 0.658)	0.645 (0.634 to 0.655)	0.641 (0.631 to 0.652)	0.591 (0.581 to 0.600)	0.610 (0.600 to 0.619)	0.606 (0.596 to 0.615)
75–84	0.616 (0.607 to 0.624)	0.614 (0.605 to 0.622)	0.613 (0.604 to 0.622)	0.570 (0.559 to 0.580)	0.594 (0.583 to 0.604)	0.590 (0.580 to 0.601)
mCCI						
0	0.862 (0.855 to 0.868)	0.862 (0.855 to 0.868)	0.861 (0.855 to 0.868)	0.812 (0.806 to 0.817)	0.825 (0.820 to 0.831)	0.824 (0.818 to 0.829)
1	0.843 (0.833 to 0.854)	0.843 (0.833 to 0.854)	0.843 (0.833 to 0.854)	0.815 (0.805 to 0.826)	0.830 (0.820 to 0.841)	0.830 (0.819 to 0.840)
2	0.787 (0.770 to 0.805)	0.788 (0.771 to 0.806)	0.789 (0.771 to 0.806)	0.704 (0.685 to 0.722)	0.729 (0.710 to 0.747)	0.728 (0.709 to 0.747)
≥ 3	0.753 (0.725 to 0.781)	0.754 (0.726 to 0.782)	0.754 (0.726 to 0.782)	0.666 (0.636 to 0.695)	0.698 (0.668 to 0.727)	0.695 (0.665 to 0.724)

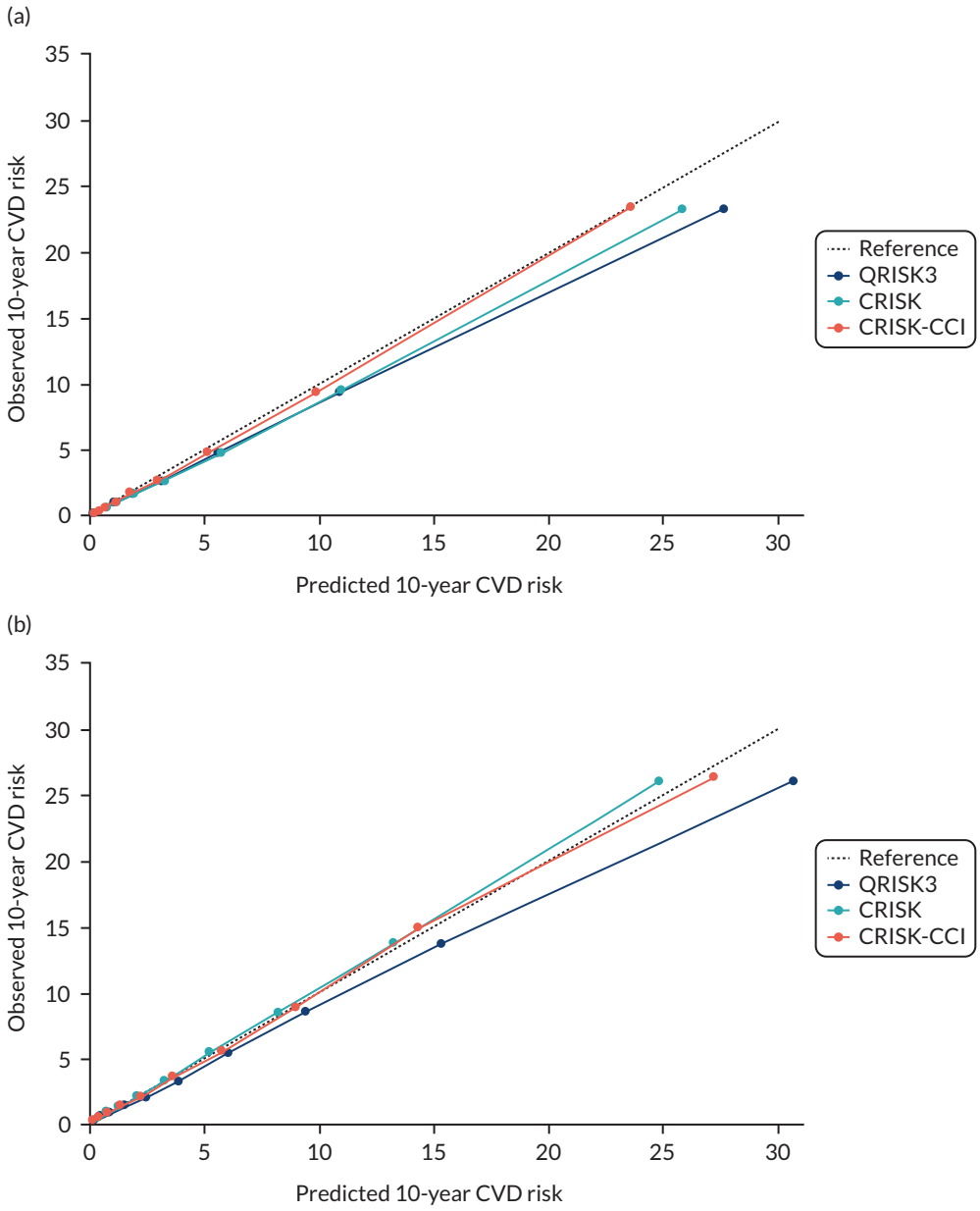


FIGURE 3 Whole-population calibration of the competing risk model with the CCI (orange), the competing risk model without the CCI (light blue) and QRISK3 (dark blue) in (a) women; and (b) men. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk.

systematically overpredicted. CRISK-CCI was better calibrated in men aged 45–64 years, although CRISK-CCI was overpredicted at the highest decile of predicted risk. CRISK and CRISK-CCI had similar calibration in older men, although CRISK-CCI had greater overprediction at higher levels of predicted risk. In men with increasing CCI, QRISK3 was the least well calibrated, with overprediction in all strata. CRISK-CCI was best calibrated in people with low comorbidity (i.e. mCCI = 0 and mCCI = 1), but had greater overprediction at higher levels of predicted risk than CRISK (see *Figure 5*).

Summary

QRISK3 external validation

At the whole-population level, QRISK3 has excellent discrimination (which is the ability of the model to distinguish people at higher or lower risk). However, as is expected when examining discrimination in subsets of the modelled population defined by strong predictors of the outcome,[72] discrimination was

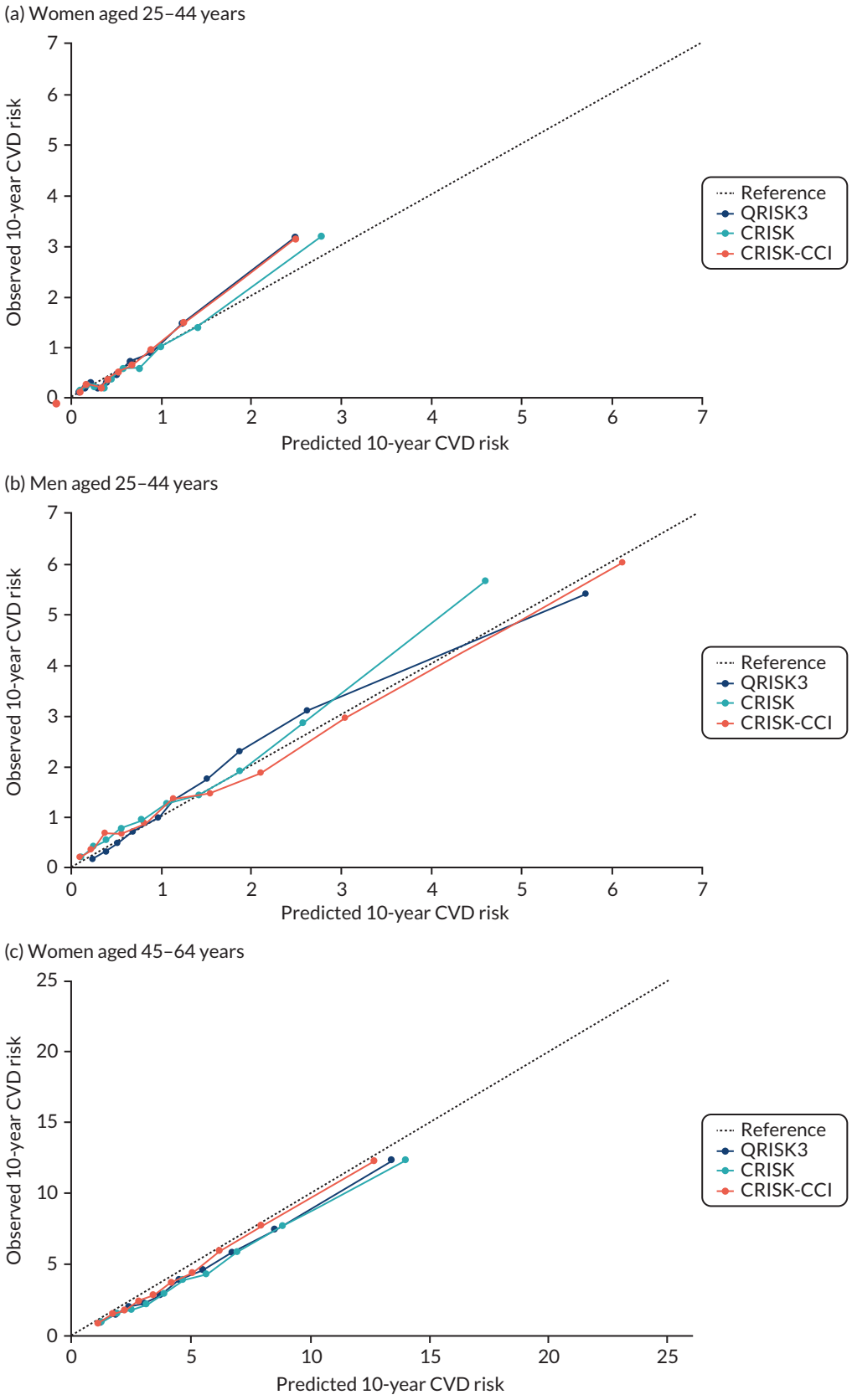
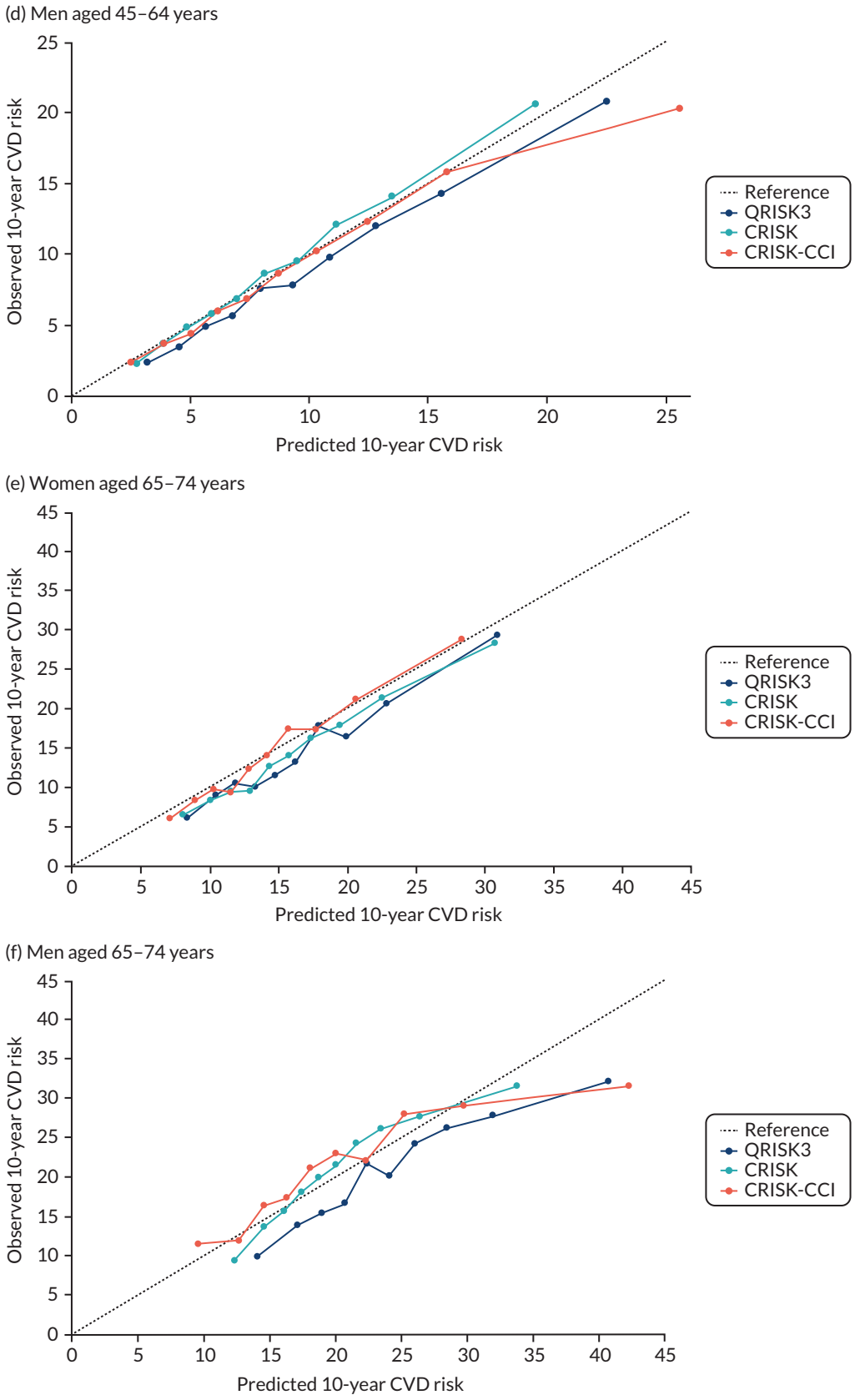


FIGURE 4 Calibration of CRISK-CCI, CRISK and QRISK3 by age group. (a) Women aged 25–44 years; (b) men aged 25–44 years; (c) women aged 45–64 years; (d) men aged 45–64 years; (e) women aged 65–74 years; (f) men aged 65–74 years; (g) women aged 75–84 years; and (h) men aged 75–84 years. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line, below the line is overprediction and above the line is underprediction. (*continued*)



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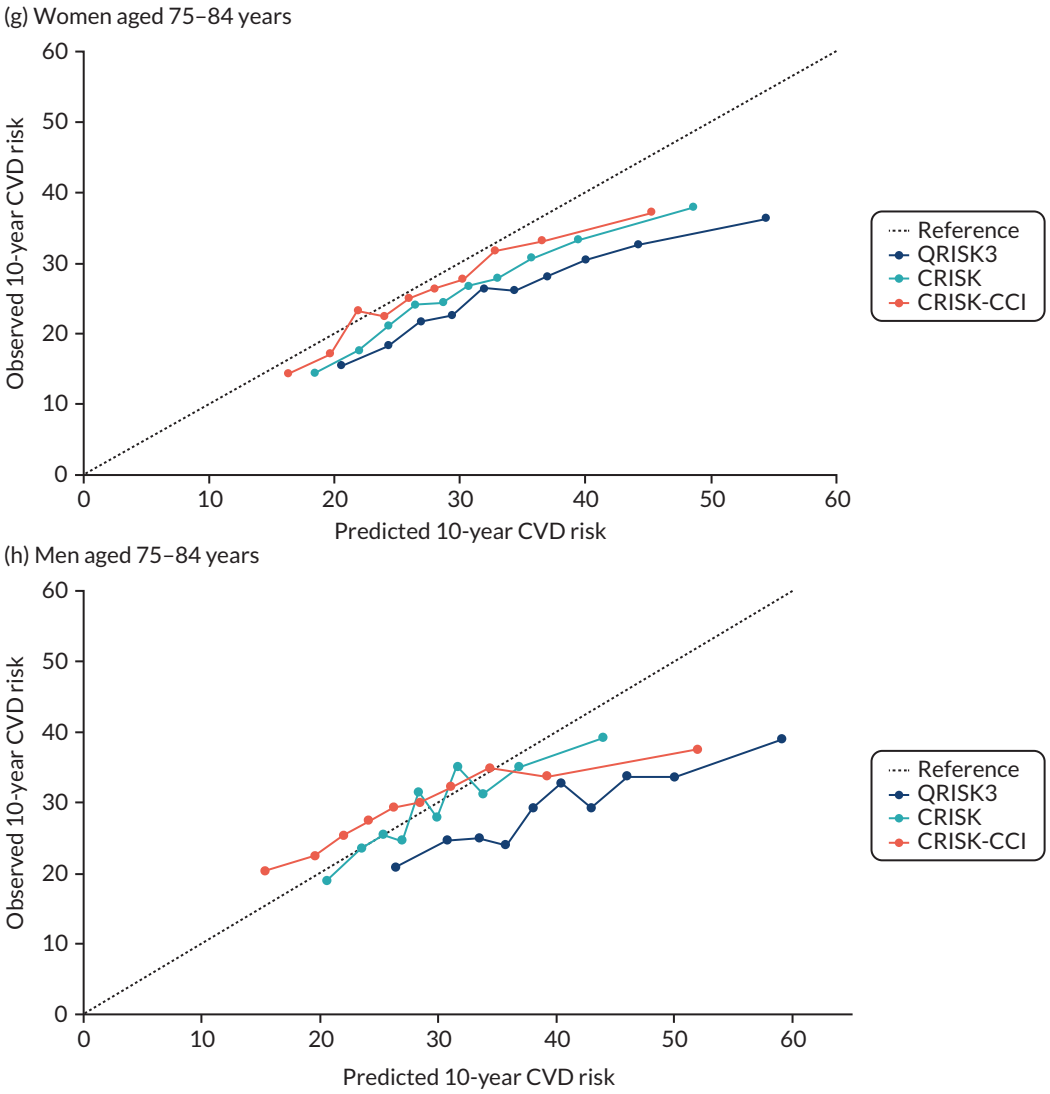

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poor to moderate when stratified by age and additionally worse when stratified by level of comorbidity (which was not a predictor in the model). Calibration is the extent to which predicted and observed event rates are similar, and it was excellent in the whole population when ignoring competing mortality risks; however, there was systematic underprediction after competing risks were accounted for. Calibration was considerably worse in older people and in people with higher levels of comorbidity, where QRISK3 systematically overpredicted risk, particularly after competing mortality risks were accounted for.

In people with diabetes, discrimination was excellent in type 1 diabetes and moderate to good in type 2 diabetes. Similar to the whole population, calibration was good, with some overprediction when ignoring competing risks, but there was more consistent overprediction once competing risks were accounted for. Similar findings were found for people with CKD, but it is important to recognise that the populations studied exclude people with prior statin prescribing, which excludes substantial numbers of people with either condition (based on statin prescribing in the primary prevention population, 27.0% of women and 49.9% of men with type 1 diabetes, 45.4% of women and 40.1% of men with type 2 diabetes, and 30.5% of women and 24.4% of men with CKD defined by Read code were excluded).

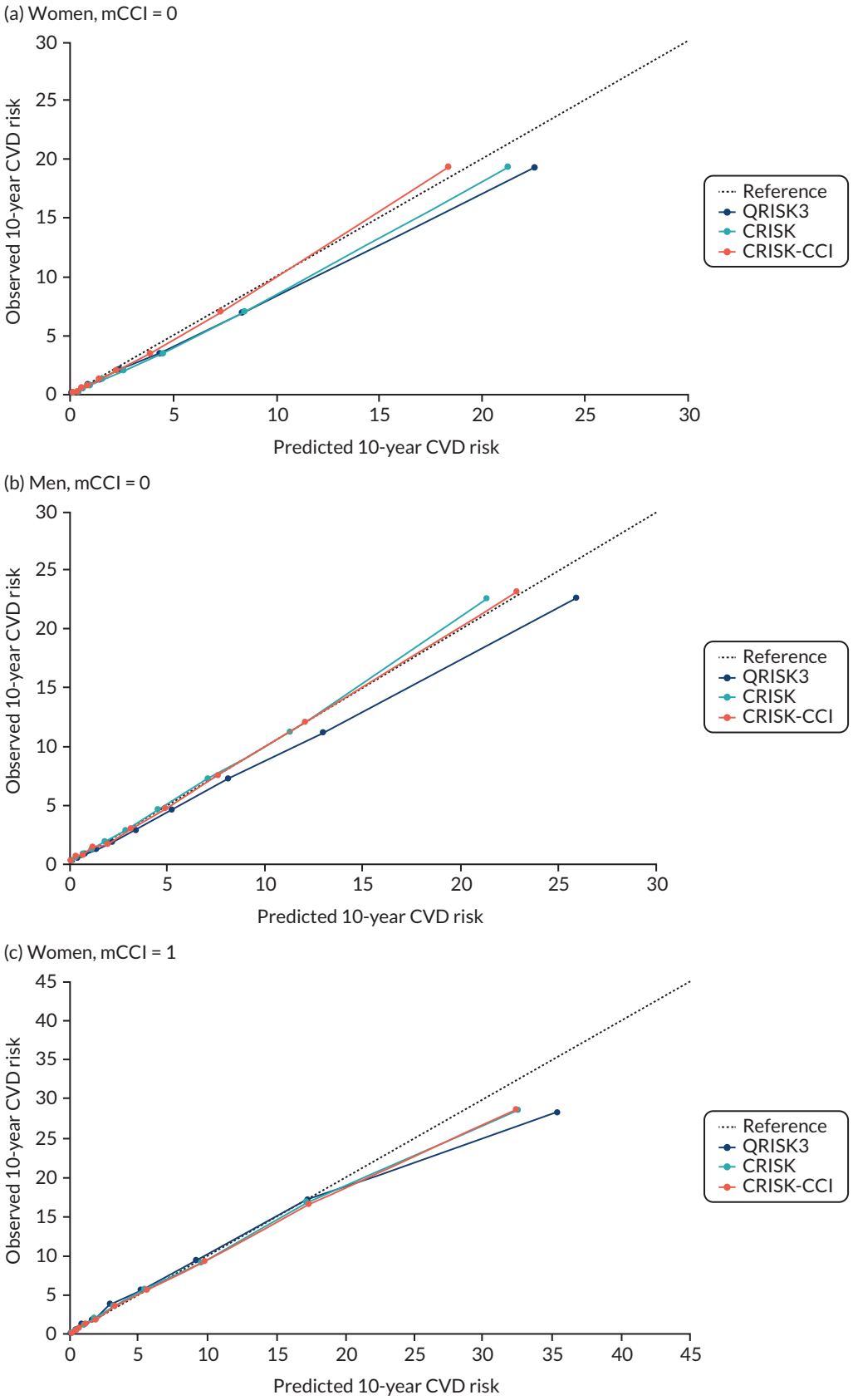
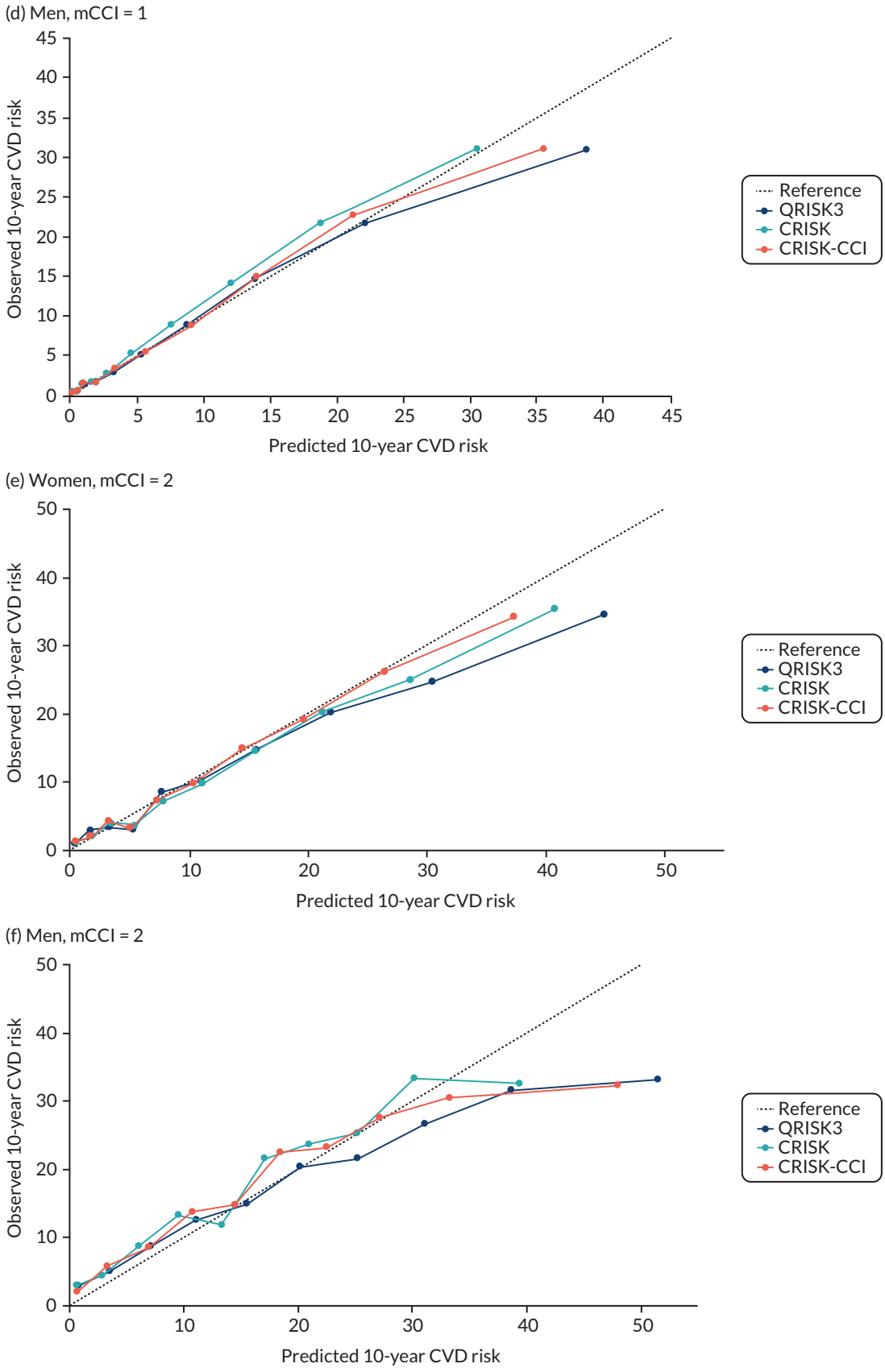


FIGURE 5 Calibration of CRISK-CCI, CRISK and QRISK3 by mCCI group. (a) Women, mCCI = 0; (b) men, mCCI = 0; (c) women, mCCI = 1; (d) men, mCCI = 1; (e) women, mCCI = 2; (f) men, mCCI = 2; (g) women, mCCI ≥ 3; and (h) men, mCCI ≥ 3. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line, below the line is overprediction and above the line is underprediction. (*continued*)



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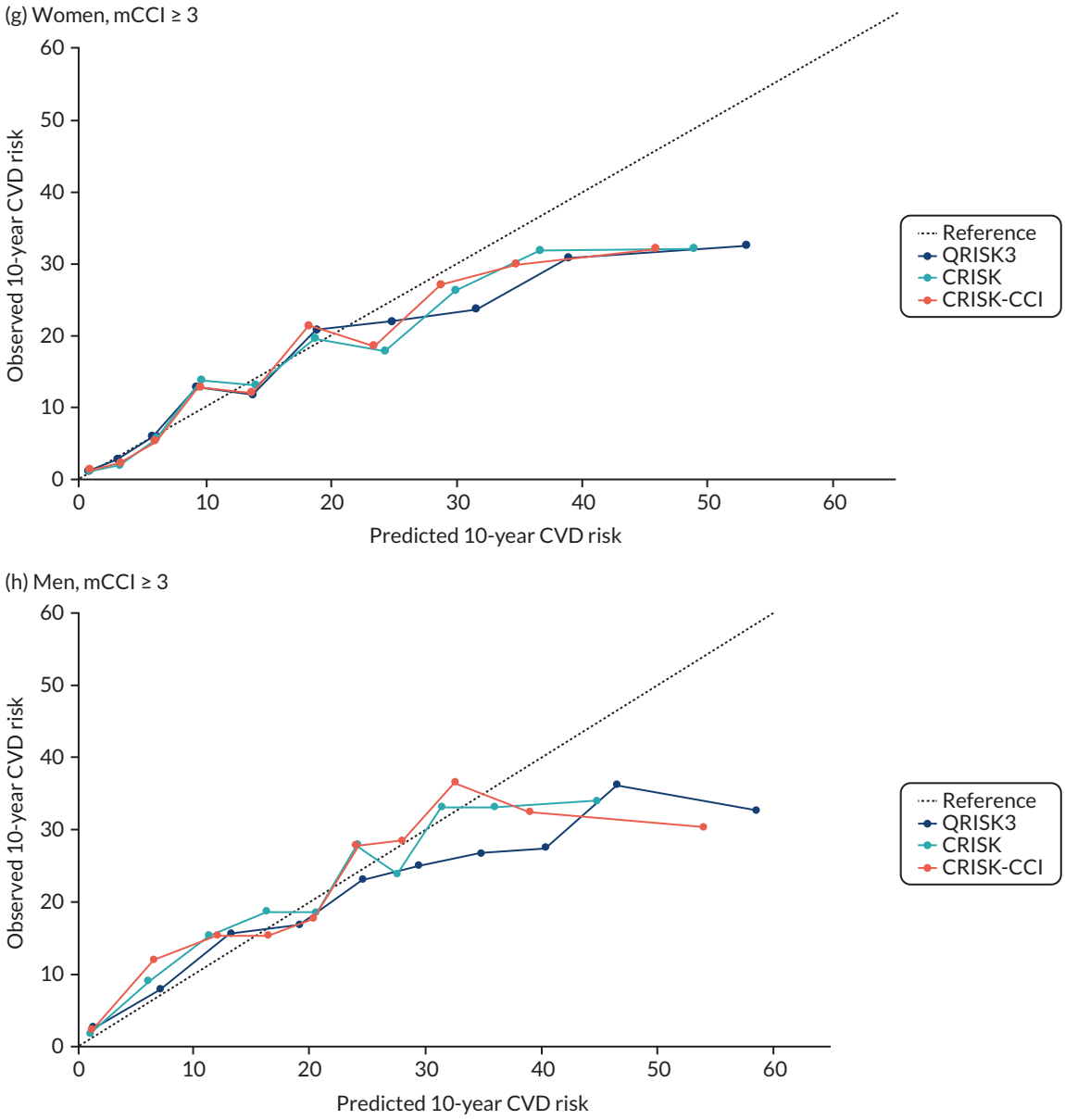


FIGURE 5 Calibration of CRISK-CCI, CRISK and QRISK3 by mCCI group. (a) Women, mCCI = 0; (b) men, mCCI = 0; (c) women, mCCI = 1; (d) men, mCCI = 1; (e) women, mCCI = 2; (f) men, mCCI = 2; (g) women, mCCI ≥ 3; and (h) men, mCCI ≥ 3. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line, below the line is overprediction and above the line is underprediction.

The published external validation of QRISK2 found excellent discrimination and calibration at the whole-population level when ignoring competing mortality risk (i.e. answering the question 'what is the risk of CVD assuming this person does not die of anything else in the next 10 years?').[15] This study found similar, but additionally found overprediction and poor calibration in people aged 75–84 years, and moderate calibration in people aged 65–74 years and in people with the highest levels of comorbidity (mCCI = 3).

Once competing mortality risk was accounted for (i.e. answering the question 'what is the risk of CVD allowing for the risk of death from something else first?'), then there was greater overprediction at the whole-population level, and particularly in older people and in people with more comorbidity. These findings are consistent with other studies examining the impact of competing risks on estimated CVD risk in people without CVD[34,73,74] and with established CVD.[75]

QRISK2 has also been shown to systematically overpredict CVD risk in a contemporary population of people with type 2 diabetes, with increasingly poor discrimination with increasing age[76] and underprediction in a contemporary population of people with type 1 diabetes.[60] This highlights that good performance at the whole-population level does not necessarily mean good performance in important subgroups,[72] and also that models derived in populations excluding prior statin prescribing are likely to be increasingly unrepresentative as statin prescribing increases.

CRISK and CRISK-CCI derivation and internal validation

The two new competing risk models derived (i.e. CRISK and CRISK-CCI) has similar excellent discrimination for CVD events as QRISK3. CRISK was better calibrated than QRISK3 (after accounting for competing mortality in derivation, but without adding any new predictors to the model) and CRISK-CCI was better calibrated again (after adding the mCCI as an additional predictor).

Two studies[74,77] in people aged ≥ 65 years have examined the impact of competing mortality risk on CVD prediction. Like this study, the two studies[74,77] also found only moderate discrimination of whole-population CVD risk prediction tools in older adults, and that newly derived competing risks models were generally better calibrated than models derived using standard Cox regression.[77] In a UK study[35] evaluating a new competing risk model against the QRISK2, differences between predicted and observed CVD risk were greatest among people with highest predicted risk, as was found in this study.

Limitations

Limitations of this study are largely those that are found in all studies using routine GP data, including the original QRISK3 derivation.[20] First, there is considerable missing data for key predictors. As with QRISK3 derivation, we used multiple imputation for missing data, but the assumption that data are missing at random is a strong one because risk factors are likely to be better recorded in people at higher CVD risk.[35] This weakness is balanced against the use of more representative population data than is found in individually recruited research cohorts where data are more complete. Second, we used a more recent index date (1 January 2014) than QRISK3 (1 January 1998), which likely means that we exclude more people with prior statin prescribing. Deriving clinical prediction tools on increasingly historical data is likely biased because CVD incidence is falling,[73] but using more recent data with greater rates of exclusion because of prior statin initiation may also be biased.

Chapter 3 External validation of QRISK-Lifetime

Background

Most cardiovascular risk prediction models use a medium-term time frame, most commonly 10 years. However, as age dominates cardiovascular risk, a potential problem of basing treatment on 10-year predicted risk is that younger people with very unfavourable risk factor profiles may not have high enough 10-year risk to be recommended for preventative treatment, even though in the longer-term their risk is very high.[27,78–80] International guidelines recommend consideration of lifetime risk in younger people alongside 10-year risk, although NICE does not.[10] The QRISK-Lifetime prediction tool was created in the same data set as QRISK2, and can be used as a standalone web-based tool[81] as well as being the risk engine underlying the Joint British Societies' risk calculator (JBS3)[79] and Heart Age[82] tools. Although lifetime tools are not currently recommended for CVD risk stratification by NICE,[10] lifetime tools have been identified as a topic to examine further in a future guideline update.[13]

Unlike QRISK2 and QRISK3, QRISK-Lifetime does account for competing mortality risk, which is further potential advantage. However, lifetime models are difficult to validate, as observational data sets only very rarely observe events over a lifetime (e.g. some analyses using the Framingham study have almost 40 years of follow-up[83]). The QRISK-Lifetime model, therefore, uses information about older people in the data set to predict what will happen to younger people in the future. There is, therefore, an assumption that observed risk in older people now will apply to younger people in several decades time, and this is a very strong assumption given the large declines in age-standardised incidence of CVD in high-income countries since the 1970s, and the unknown effect of changing risk factors more recently (with declines in smoking in high-income countries, but increases in obesity, type 2 diabetes and sedentary behaviour). Similar issues (e.g. very long follow-up) apply to data sets like the Framingham study, as, by definition, patients enter the cohort in the distant past. Given available UK data, external validation is, therefore, in practice only possible over shorter time horizons. For example, internal validation of QRISK-Lifetime in the original derivation study examined predictive performance over a 10-year time horizon and compared with QRISK2, which predicts over the same time horizon.[27] However, if tool performance is poorly calibrated in different age groups, then it is possible to infer performance over a lifetime. Although there have been studies of reclassification using QRISK-Lifetime-predicted lifetime risk compared with QRISK3 10-year predicted risk,[78] to our knowledge there has not been an independent external validation.

This chapter reports findings in relation to objective 3 (i.e. to externally validate the QRISK-Lifetime risk prediction tool for primary prevention of CVD), examining discrimination and calibration over a 10-year time horizon and the characteristics of those reclassified as high risk using QRISK-Lifetime rather than QRISK3.

Methods

Data sources, outcome definition, other variable definitions and missing data

The same data set used for QRISK3 external validation was used (see *Chapter 2*, *Methods*), with the same variation in methods applying (i.e. a cohort entry date of 1 January 2004 vs. 1 January 1998 for QRISK-Lifetime, our implementation did not allow the use of future cholesterol values and Townsend deprivation scores were fitted as the median of vigintiles of Townsend score).

Analytical methods

The lifetime (i.e. to age 95 years) and 10-year risk of experiencing a cardiovascular event was calculated for each patient using publicly available QRISK-Lifetime 2011 software (under GNU Lesser General Public Licence version 3) without recalibration. As lifetime risk is not observed in the validation data set, the performance of the risk score was assessed by examining discrimination and calibration of the model using the same methods as for QRISK3 external validation (see *Chapter 2*, *Methods*) over a 10-year time horizon, as was carried out in the original derivation and internal validation study.[27] For both men and women, calibration was evaluated in the whole population and in prespecified subgroups of age and mCCI. Calibration refers to how closely predicted risk and observed probabilities agree at group level. As QRISK-Lifetime accounts for competing mortality risk, we evaluated calibration using only the Aalen–Johansen estimator of observed risk in censored survival data (i.e. an extension of the Kaplan–Meier estimator, which allows for competing events, non-CVD death in this case).[84]

Clinical guideline recommendations for primary preventative treatment of CVD classify patients in relation to thresholds of predicted risk. In England and Wales, NICE-recommend treatment if 10-year predicted CVD risk is ≥ 10%. Consistent with the validation of QRISK-Lifetime over a 10-year time horizon, we examined changes in which patients were recommended for treatment based on either a QRISK3 or QRISK-Lifetime 10-year predicted risk of ≥ 10%.

However, there is no recommended threshold of lifetime risk at which to offer treatment,[10] although NICE has signalled that consideration of lifetime risk models is of interest in any future guideline update.[13] Therefore, we additionally calculated the proportion of men and women recommended for treatment by QRISK3 at the 10% threshold, and used a cut-off point of QRISK-Lifetime-predicted lifetime risk above which exactly the same proportion of participants lay.

For both comparisons (i.e. QRISK3 and QRISK-Lifetime 10-year prediction > 10%; and QRISK3 prediction > 10% and matched number of participants with the highest lifetime predicted risk), we examined the characteristics of patients recommended for treatment, the observed risk of CVD at 10 years, and the number needed to treat (NNT) to prevent one new CVD event assuming all people recommended for treatment actually took a statin and with a relative risk reduction of 25% for new CVD events. All models were fitted in R and Stata.

Results 1: external validation of QRISK-Lifetime

There were 1,260,329 women and 1,223,265 men aged 30–84 years in the external validation data set, with a mean age of 49.3 years for women and 47.6 years for men (see *Appendix 2*, *Table 31*). Baseline characteristics were similar to QRISK-Lifetime internal validation, with the exception of the external validation data set having somewhat fewer people with a recorded family history of premature CVD and somewhat more people with treated hypertension and CKD.

Evaluated at 10 years' follow-up, QRISK-Lifetime had excellent discrimination in the whole population of both women (Harrell's *c*-statistic 0.844, 95% CI 0.841 to 0.847) and men (Harrell's *c*-statistic 0.808, 95% CI 0.806 to 0.811), similar to the QRISK-Lifetime internal validation [area under the receiver operating curve (AUROC): women, 0.842; men, 0.828] (*Table 3*).[27] Explained variation in women was 53.3% compared with 45.5% in men. Stratified by age, discrimination varied from good in people aged 30–44 years (Harrell's *c*-statistic: women, 0.714; men, 0.714) to poor in people aged 75–84 years (Harrell's *c*-statistic: women, 0.578; men, 0.556), and explained variation progressively declined with age. Stratified by comorbidity, discrimination varied from excellent in people with low comorbidity (mCCI = 0 Harrell's *c*-statistic: women, 0.844; men, 0.803) to moderate to good in people with high comorbidity (mCCI ≥ 3 Harrell's *c*-statistic: women, 0.724; men, 0.656).

TABLE 3 Discrimination of QRISK-Lifetime (evaluated at 10 years)

	Women			Men		
Patient group	**Harrell's *c*-statistic (95% CI)**	**D-statistic (95% CI)**	**R^2-statistic (95% CI)**	**Harrell's *c*-statistic (95% CI)**	**D-statistic (95% CI)**	**R^2-statistic (95% CI)**
All patients	0.844 (0.841 to 0.847)	2.19 (2.17 to 2.21)	53.3 (52.9 to 53.7)	0.808 (0.806 to 0.811)	1.87 (1.85 to 1.89)	45.5 (45.1 to 46.0)
Age group (years)						
30–44	0.714 (0.703 to 0.725)	1.33 (1.26 to 1.39)	29.6 (27.6 to 31.7)	0.714 (0.706 to 0.722)	1.24 (1.20 to 1.29)	26.9 (25.6 to 28.3)
45–64	0.692 (0.687 to 0.698)	1.14 (1.10 to 1.17)	23.5 (22.5 to 24.6)	0.671 (0.667 to 0.675)	0.97 (0.94 to 0.99)	18.2 (17.4 to 19.1)
65–74	0.631 (0.625 to 0.637)	0.75 (0.71 to 0.79)	11.8 (10.6 to 13.0)	0.597 (0.591 to 0.603)	0.54 (0.51 to 0.58)	6.6 (5.8 to 7.3)
75–84	0.578 (0.573 to 0.583)	0.44 (0.40 to 0.49)	4.5 (3.6 to 5.5)	0.556 (0.549 to 0.562)	0.32 (0.28 to 0.36)	2.4 (1.9 to 3.0)
mCCI						
0	0.844 (0.840 to 0.848)	2.19 (2.17 to 2.21)	53.4 (52.8 to 53.9)	0.803 (0.800 to 0.806)	1.82 (1.80 to 1.84)	44.1 (43.6 to 44.6)
1	0.820 (0.814 to 0.826)	1.95 (1.92 to 1.99)	47.6 (46.7 to 48.5)	0.798 (0.792 to 0.804)	1.76 (1.72 to 1.80)	42.4 (41.3 to 43.5)
2	0.768 (0.758 to 0.779)	1.54 (1.49 to 1.60)	36.3 (34.6 to 37.9)	0.701 (0.690 to 0.711)	1.13 (1.07 to 1.19)	23.4 (21.5 to 25.3)
≥ 3	0.724 (0.708 to 0.740)	1.29 (1.21 to 1.38)	28.5 (25.8 to 31.2)	0.656 (0.639 to 0.673)	0.91 (0.82 to 0.99)	16.4 (13.8 to 19.1)

Source: Livingstone *et al.*[49]

In the whole population, calibration was reasonable at lower levels of predicted risk for both men and women, but there was considerable overprediction at higher levels of predicted risk (*Figure 6*). Stratified by age, in both men and women, there was some underprediction in people aged 30–44 years, calibration was good in people aged 45–64 years and there was considerable underprediction in older people (see *Figure 6*). Stratified by comorbidity, in both men and women, there was underprediction at higher levels of predicted risk in people with low comorbidity (mCCI = 0) and consistent underprediction in people with higher comorbidity (see *Figure 6*).

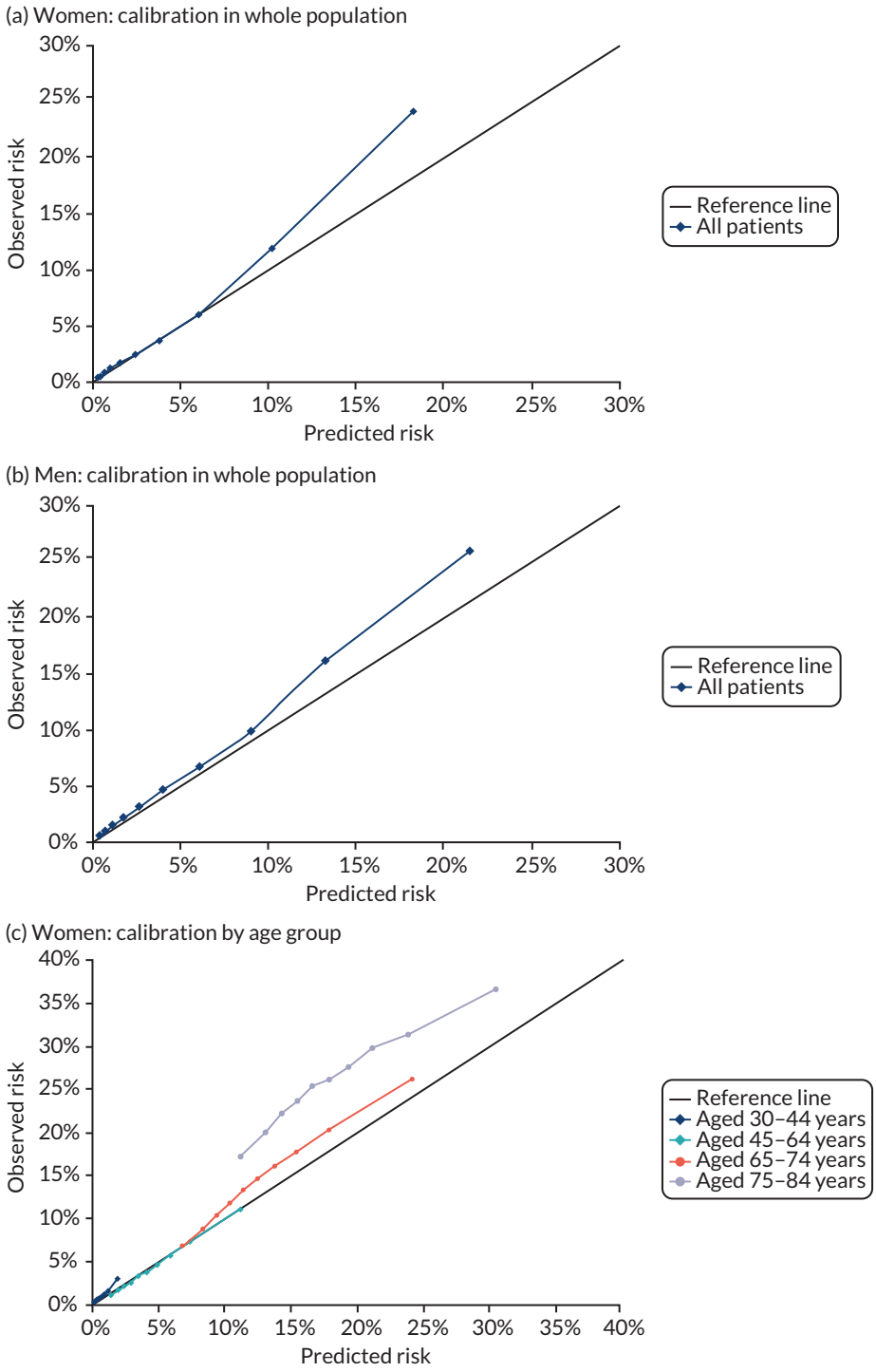
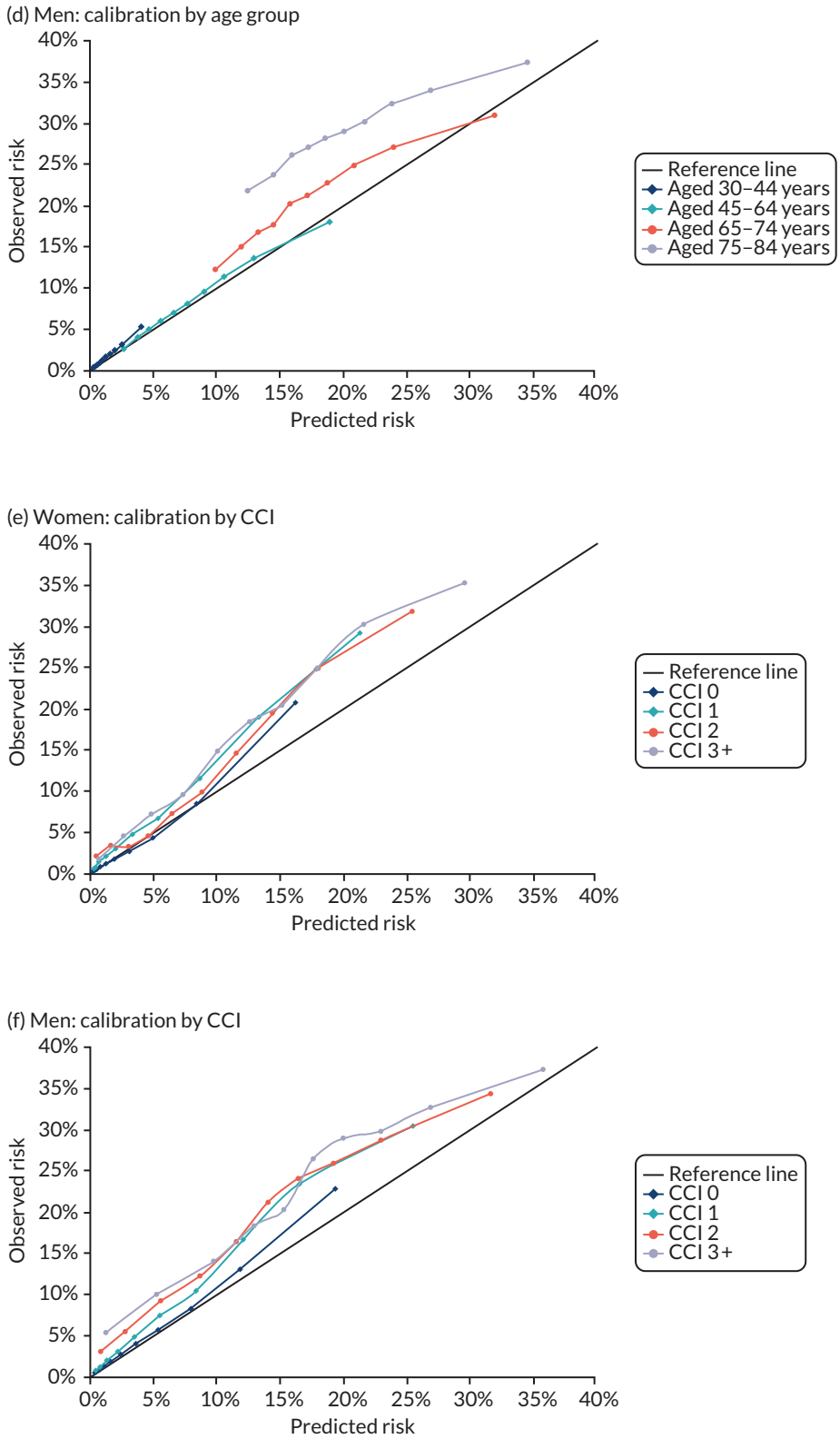


FIGURE 6 Calibration of QRISK-Lifetime in women and men (evaluated at 10 years): whole population and stratified by age group and CCI score. (a) Women: calibration in whole population; (b) men: calibration in whole population; (c) women: calibration by age group; (d) men: calibration by age group; (e) women: calibration by CCI; and (f) men: calibration by CCI. A prediction point/line above the reference line means that the risk score underpredicts and a predicted point/line below the reference line means that the risk score overpredicts. Source: Livingstone *et al.*[49] (*continued*)



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Results 2: reclassification of study participants by QRISK-Lifetime compared with QRISK3

Reclassification using QRISK-Lifetime constrained to 10-year versus QRISK3 10-year prediction

In the first reclassification analysis examining people with 10-year predicted CVD risk > 10% using QRISK-Lifetime and QRISK3, QRISK-Lifetime classified fewer people as eligible to be offered a statin than QRISK3 (*Table 4*). QRISK-Lifetime classified 194,411 (15.4%) women as high risk, compared with 239,396 (19.0%) women classified as high risk by QRISK3. QRISK-Lifetime classified 276,369 (22.6%) men as high risk, compared with 341,962 (28.0%) men classified as high risk by QRISK3. For women, 15.1% were classified as high risk by both tools, 3.9% were classified as high risk by QRISK3 only and 0.3% were classified as high risk by QRISK-Lifetime only, over 10 years. For men, 21.9% were classified as high risk by both tools, 6.1% were classified as high risk by QRISK3 only and 0.7% were classified as high risk by QRISK-Lifetime only, over 10 years.

Based on 10-year risk prediction, the characteristics of people classified as high risk by each tool were similar (*Table 5*). Fewer people were recommended for treatment by QRISK-Lifetime and there were fewer observed events in people recommended for treatment by QRISK-Lifetime (women, 25,461 vs. 28,373; men, 33,450 vs. 37,026), but the percentage of people experiencing an event was higher (women, 13.2% vs. 11.9%; men, 12.1% vs. 10.8%). Among people recommended for treatment with a statin, the estimated NNT from statin prescription to prevent one event was 30 and 34 in women, and 33 and 37 in men, for QRISK-Lifetime and QRISK3, respectively (see *Table 5*).

Reclassification using QRISK-Lifetime lifetime risk versus QRISK3 10-year prediction

By design, the comparison with QRISK-Lifetime predicting to age 95 years (i.e. lifetime risk) was constrained to include 19.0% of women and 28.0% of men at the highest predicted lifetime risk (i.e. the same proportion of people identified as high risk based on QRISK3 10-year prediction) (see *Table 4*). Only 5.3% of women were identified as high risk by both QRISK3 and QRISK-Lifetime predicting to age 95 years, with a different 13.7% of women identified as high risk by one or other of the prediction tools. For men, 8.9% were identified as high risk by both prediction tools and a different 19.1% of men by one or other of the tools.

TABLE 4 Reclassification between QRISK3 and QRISK-Lifetime based on 10-year risk prediction for both

	Women		Men	
	QRISK-Lifetime < 10% at 10 years	**QRISK-Lifetime ≥ 10% at 10 years**	**QRISK-Lifetime < 10% at 10 years**	**QRISK-Lifetime ≥ 10% at 10 years**
Based on 10-year risk prediction for both				
QRISK3 < 10%	1,017,314 (80.7)	3619 (0.3)	872,474 (71.3)	8829 (0.7)
QRISK3 ≥ 10%	48,604 (3.9)	190,792 (15.1)	74,422 (6.1)	267,540 (21.9)
	QRISK-Lifetime < 32.9%[a]	**QRISK-Lifetime ≥ 32.9%[a]**	**QRISK-Lifetime < 39.6%[a]**	**QRISK-Lifetime ≥ 39.6%[a]**
Based on QRISK3 10-year risk prediction and QRISK-Lifetime lifetime risk (matched numbers of patients with QRISK3)				
QRISK3 < 10%	847,786 (67.3)	173,147 (13.7)	647,949 (53.0)	233,354 (19.1)
QRISK3 ≥ 10%	173,147 (13.7)	66,249 (5.3)	233,354 (19.1)	108,608 (8.9)

a QRISK-Lifetime threshold defined to include the same number of patients recommended for treatment as QRISK3 10-year risk ≥ 10%.

Notes

Percentages are the per cent of all patients in each of the four cross-classifications.
Source: Livingstone *et al.*[49]

TABLE 5 Characteristics of those recommended for treatment by QRISK3 10-year prediction, QRISK-Lifetime 10-year prediction and QRISK-Lifetime lifetime prediction (matched numbers of patients to QRISK3)

Patient group	Number (%) recommended for treatment	Number (%) with a CVD event	NNT[a]	Mean (SD) age	Mean (SD) TC : HDL	Mean (SD) SBP (mmHg)	Mean (SD) BMI (kg/m^2)	Treated HT, % (95% CI)	Current smoker, % (95% CI)	Family history of premature CVD, % (95% CI)	Minority ethnic background, % (95% CI)
Women											
QRISK3 ≥ 10% predicted risk at 10 years	239,396 (19.0)	28,373 (11.9)	34	71.3 (8.2)	3.8 (0.8)	143.9 (17.0)	26.8 (4.5)	31.9 (31.7 to 32.1)	18.1 (17.9 to 18.2)	6.3 (6.2 to 6.4)	3.0 (2.9 to 3.1)
QRISK-Lifetime ≥ 10% predicted risk at 10 years	194,411 (15.4)	25,641 (13.2)	30	73.3 (7.0)	3.8 (0.8)	145.0 (17.0)	26.8 (4.4)	36.2 (36.0 to 36.4)	15.9 (15.7 to 16.0)	7.8 (7.7 to 7.9)	3.2 (3.1 to 3.2)
QRISK-Lifetime ≥ 32.9% predicted lifetime risk[b]	239,396 (19.0)	9652 (4.0)	99	50.5 (12.6)	4.0 (1.1)	134.9 (20.0)	28.9 (5.6)	29.4 (29.2 to 29.6)	21.3 (21.2 to 21.5)	36.3 (36.2 to 36.5)	20.8 (20.6 to 20.9)
Men											
QRISK3 ≥ 10% predicted risk at 10 years	341,962 (28.0)	37,026 (10.8)	37	63.8 (9.6)	4.3 (0.9)	140.2 (15.5)	27.1 (3.7)	19.6 (19.5 to 19.8)	26.1 (26.0 to 26.2)	7.2 (7.1 to 7.2)	3.2 (3.1 to 3.2)
QRISK-Lifetime ≥ 10% predicted risk at 10 years	276,369 (22.6)	33,450 (12.1)	33	66.2 (8.5)	4.3 (0.9)	140.8 (15.6)	27.1 (3.7)	22.3 (22.2 to 22.5)	23.4 (23.2 to 23.6)	8.3 (8.2 to 8.4)	3.3 (3.3 to 3.4)
QRISK-Lifetime ≥ 32.9% predicted lifetime risk[b]	341,962 (28.0)	14,725 (4.3)	100	46.3 (10.4)	4.9 (0.9)	135.7 (15.2)	29.1 (4.1)	15.0 (14.9 to 15.2)	26.4 (26.2 to 26.5)	20.0 (19.9 to 20.2)	13.1 (13.0 to 13.2)

HT, hypertension; SD, standard deviation.
a Assuming a 25% risk reduction with primary prevention using statins, with treatment taken by all people recommended for treatment.
b QRISK-Lifetime threshold defined to include the same number of patients recommended for treatment as QRISK3 10-year risk ≥ 10%.
Source: Livingstone *et al.*[49]

Compared with people identified as high risk by QRISK3 10-year prediction, people with the highest predicted lifetime risk were much younger, had a lower mean SBP and had a somewhat higher mean TC : HDL and BMI. In addition, a lower proportion of people with the highest predicted lifetime risk had treated hypertension and a much higher proportion had a family history of premature CVD and were from a minority ethnic background (see *Table 5*). Compared with people recommended for treatment based on 10-year predicted risk, there were fewer CVD events observed in people at the highest predicted lifetime risk [women, 9652 (4.0%) vs. 28,373 (11.9%); men, 14,725 (4.3%) vs. 37,026 (10.8%)]. For QRISK-Lifetime predicting to age 95 years, the estimated NNT to prevent one CVD event from statin treatment was 99 and 100 in women and men, respectively, compared with 34 and 37 in women and men, respectively, among those with > 10% 10-year QRISK3-predicted risk (see *Table 5*).

Summary

QRISK-Lifetime external validation

It is essentially impossible to validate lifetime risk models because lifetime follow-up of observed events either is not available or would be so historical that it would be a poor guide to performance of the model in a contemporary population.[60,85] Similar to the original internal validation,[27] we evaluated QRISK-Lifetime over a 10-year prediction horizon. Within this constraint, QRISK-Lifetime had excellent discrimination in the whole population; however, as with QRISK3, discrimination was poor to moderate within the age strata, and moderate within the comorbidity strata. Calibration plots showed some underprediction in the whole population, with large underprediction in older people and people with multimorbidity at higher levels of predicted risk.

Comparing people recommended for treatment at a 10-year 10% risk threshold, QRISK-Lifetime (predicting over 10 years) recommended fewer people for statin treatment (i.e. 15.4% of women and 22.6% of men) than QRISK3 (i.e. 19.0% of women and 28.0% of men), although the people recommended experienced slightly more CVD events and the estimated NNT to prevent one CVD event was slightly lower for QRISK-Lifetime. Characteristics of people recommended for treatment over a 10-year prediction horizon were broadly similar.

Comparing people recommended for treatment by QRISK3-predicted 10-year risk ≥ 10% compared with the same proportion at highest estimated lifetime risk by QRISK-Lifetime, there was only a small overlap between the populations at highest predicted risk by the different tools. By design, each tool 'recommended' 19.0% of women and 28.0% of men for treatment. Only 5.3% of women and 8.9% of men were recommended for treatment by both tools, and the people recommended for treatment were considerably different, as other studies have found.[27,78] People with highest predicted lifetime risk were considerably younger, were more likely to have a family history of premature CVD and were more likely to be from a minority ethnic background. Over 10 years, people with highest predicted lifetime risk experienced many fewer CVD events (as expected given age differences), with people at highest predicted lifetime risk having an estimated NNT (with a statin to prevent one CVD event) approximately three times larger than for people recommended for treatment by QRISK3 (in women, QRISK-Lifetime highest risk NNT = 99 vs. QRISK3 risk > 10% NNT = 34; in men, QRISK-Lifetime highest risk NNT = 100 vs. QRISK3 risk > 10% NNT = 37). There is, therefore, a considerable leap of faith involved in treating based on lifetime risk, as the medium-term (10-year) benefit is considerably lower.

Limitations

This study has the same limitations as those already described in *Chapter 2*, *Limitations*, for any routine data study, but two particular limitations specifically apply. First, as with previous studies,[35,67] we used multiple imputation, but the assumption that data are missing at random may be incorrect, and this is probably more likely to apply in younger people (i.e. the key target population for lifetime CVD risk prediction), as CVD risk assessment (particularly measurement of cholesterol) is likely to be carried out in people who are already suspected to be high risk.[35] Second, evaluating lifetime risk in

a study with relatively short follow-up is intrinsically problematic. In this study, median follow-up of study participants was 5.7 years (interquartile range 2.2–10.2) years in women and 5.2 (interquartile range 2.0–9.3) years in men. The QRISK-Lifetime derivation paper does not state follow-up time,[27] but follow-up time in this study is similar to follow-up in QRISK2 derivation, which uses a similar data set to QRISK-Lifetime.[86] Lifetime risk is, therefore, being estimated and evaluated from relatively short periods of observation. However, lifetime risk is estimated by assuming that future risk beyond the period of observation will be the same as that observed for older people during the period of observation. As QRISK-Lifetime systematically underpredicts CVD risk over the period of observation, then lifetime estimates must also underpredict. More generally, however, it is a very strong assumption that age-specific CVD incidence will be stable over the next few decades, given falling CVD incidence over the last few decades and large increases in obesity, sedentary behaviour and diabetes in the last two decades.

Chapter 4 Fracture risk prediction: external validation of QFracture-2012 and derivation and internal validation of a new competing risk model (CFracture)

Background

In older people, fragility or low-impact fractures are a common cause of morbidity, disability and (for fractured neck of femur) death. Osteoporosis and osteopenia are an important driver of this fracture risk, and guidelines internationally recommend treatment with bisphosphonates for people at high risk of fracture.[12,87–89] In the UK, guidelines recommend using a fracture risk prediction tool in older people and in middle-aged people who have risk factors for fracture, with bone mineral density measurement reserved for further risk stratification in people at intermediate risk.[87,89] In the USA, guidelines recommend similar risk stratification for middle-aged people, but additional routine use of bone mineral density measurement in older people.[90]

There have been a number of fracture risk prediction tools created, and three tools (i.e. QFracture-2012, FRAX and the Garvan Fracture Risk Calculator) have been subject to substantial external validation,[91,92] although for FRAX this is limited by the prediction equation not being published.[93] The first version of QFracture-2012[17] was externally validated by the developers[19] and independently externally validated in a different UK GP data set,[18] and it was found to have excellent discrimination and calibration. The QFracture-2012 algorithm has been externally validated in an Israeli data set,[92] which found excellent discrimination but poor calibration with systematic underprediction of fracture risk. At the time the research was done, the QFracture-2016 algorithm had not been published, and it has not yet been externally validated in a general primary care population[94] FRAX has been more extensively validated; however, the underlying algorithm has never been published and so most validation is by the developers. Across all studies, FRAX discrimination appears good, but calibration is rarely assessed.[22,91] FRAX was validated in the same Israeli study[92] that examined QFracture-2012 performance, but using relatively crude categorisation of FRAX predicted risk, which was all that could be estimated given lack of access to the underlying full algorithm. Like QFracture-2012, this study[92] found evidence of considerable underprediction of risk by FRAX. One reason for the difference in calibration observed between the UK and Israeli external validations may be in the definition of fracture, with QFracture-2012 derivation and the UK external validation being based on fractures recorded in GP electronic health record and death certificate data, whereas the Israeli study also included fractures recorded in hospital data (and is, therefore, more likely to be complete).

In the UK, NICE recommends the use of either QFracture-2012 or FRAX, but acknowledges that the two tools can give very different estimates for individuals,[12,87] with FRAX overpredicting fracture risk when fracture ascertainment used the same method as QFracture-2012 derivation.[17,87,95] Two possible reasons for the differences are (1) FRAX accounting for competing mortality risk, whereas QFracture-2012 does not (therefore, QFracture-2012 would be expected to have generally higher predicted risk than FRAX as a result) and (2) differences in how fractures were measured in the derivation of each prediction tool (QFracture-2012 fractures are ascertained using codes in GP records and mortality data,[26] whereas FRAX fractures are ascertained by self-report and hospital records[28]).

Overestimation of fracture risk by not accounting for competing risk is, in principle, more likely for QFracture-2012 than for QRISK3 because QFracture-2012 predictions are made for people aged up to 99 years, compared with 84 years for QRISK3, and because fracture is a much less common cause of

death than CVD (and, therefore, a larger number of deaths are a competing risk rather than a predicted event).[67,96,97] This chapter reports findings for fracture risk prediction models in relation to objectives 1 and 2, as follows:

1. To externally validate the recommended risk prediction tools for primary prevention of CVD (QRISK3), including performance in important subgroups, and for osteoporotic fracture (QFracture-2012).
2. To derive and internally validate new-incident CVD (and osteoporotic fracture) risk prediction models, accounting for competing risks of death, and compare performance with existing risk prediction models.

Methods

Data sources

We used the same data from CPRD GOLD as for the CVD risk modelling.[66] These data are similar to data in the QFracture-2012 derivation data set in terms of their inclusion of linked primary care and mortality data, but the CPRD GOLD data used also has linked hospital admission data, which we used for fracture ascertainment.

Identical to QRISK3 derivation and internal validation, patients were eligible for inclusion if they:

- were permanently registered with a general practice, contributing up-to-standard data for at least 1 year and with consent to link GP data to hospital discharge (HES admitted patient care) and mortality (ONS mortality registration) data
- were aged ≥ 30 years and < 100 years.

Cohort entry was defined as the latest date of an individual's date of registration plus 1 year, the individual's 30th birthday or 1 January 2004. Cohort exit was defined as the earliest of:

- the first MOF or first hip fracture (two distinct outcomes are modelled)
- deregistration from their participating general practice
- date of last data collection from their participating general practice
- end-of-study follow-up on 31 March 2016.

All outcomes and predictors are recorded blind to the study hypothesis because they are recorded as part of routine clinical care.

Sample size

The sample size is fixed by the size of the CPRD GOLD data set. No formal power calculation was, therefore, carried out, as the calculation could not alter study design and the available sample size was considered more than sufficient for the purpose.[54]

Outcome definition

QFracture-2012 has separate models to predict two outcomes (i.e. MOF and hip fracture)[26] and both models were validated. In this study, MOF was defined as hip, vertebral, wrist, proximal humeral or osteoporotic fractures leading to hospital admission ascertained from codes in the GP electronic health record (using Read codes), HES discharge diagnoses (ICD-10 codes) or ONS death registration (ICD-10 codes). QFracture-2012 does not publish lists of Read codes used to define these outcomes and, therefore, we used published codesets where available[98] and otherwise derived our own (see *Appendix 3*, *Tables 32* and *33*).

Other variable definitions

We implemented the published QFracture-2012 risk model (under GNU Lesser General Public Licence version 3) and calculated QFracture-2012-predicted 10-year risk of a MOF and the risk of a hip fracture for all patients in our cohort. As with fracture outcomes, we derived codesets for each predictor (see *Appendix 3*, *Tables 34–36*), which were based on published codesets where available.[98]

There were two differences in our implementation from QFracture-2012 derivation. First, in our data set, Townsend deprivation score was available as vigintiles (twentieths) only, rather than as raw values (to minimise disclosure), and so for this variable we fitted the median Townsend score of each vigintile (as with the CVD models described previously). Second, QFracture-2012 allowed values such as BMI recorded after the date of study entry but before any fracture outcome to be used in prediction, whereas in this analysis we restricted predictor values to those recorded before study entry to avoid using future information in prediction.

In addition to QFracture-2012, we calculated the CCI for each patient at baseline based on primary care Read codes. As with the CVD models, CCI was used only to stratify the analysis of discrimination and calibration by level of comorbidity (i.e. CCI score grouped into 0, 1, 2 and ≥ 3).

Missing data

The extent and management of missing data are detailed in *Appendix 4*, *Table 37*. As with QFracture-2012 derivation, patients with missing Townsend deprivation score were excluded from the cohort and patients with missing ethnicity were assumed to be white. For missing BMI, smoking status and alcohol status, multivariate imputation via chained equations[68] was used to generate five imputed data sets. These data sets were then combined using Rubin's rules[69] to give summary point estimates, with confidence limits reflecting the uncertainty associated with imputing missing values. Reflecting that morbidity and prescribing recording in CPRD is generally good, and consistent with QFracture-2012 derivation, morbidities and prescribing variables used in the prediction score were assumed to be absent if not recorded.[66,99]

Analytical methods: external validation

The performance of the QFracture-2012 risk score was assessed by examining discrimination and calibration in the same way as for the QRISK3 external validation (see *Chapter 2*, *Methods*). Discrimination was primarily evaluated using the truncated version of Harrell's *c*-statistic to include only pairs where the earliest survival time is no later than 10 years after entry. A *c*-statistic of 0.5 indicates discrimination no better than chance, whereas a *c*-statistic of 1 indicates perfect discrimination. Evaluating how good discrimination is for values between 0.5 and 1 is arbitrary and involves judgement. We considered *c*-statistic values of 0.5–0.599 poor, values of 0.6–0.699 moderate, values of 0.7–0.799 good and values ≥ 0.8 excellent. In addition, we calculated the D-statistic of Royston and Sauerbrei (where higher values indicate better discrimination, and a difference of ≥ 0.1 is suggested as indicating meaningfully different discrimination)[70] and a related R^2-statistic appropriate for estimating explained variation for censored survival data.[71] Calibration was assessed for 10 equal-sized groups (deciles) of participants ranked by predicted risk, by plotting observed proportions versus predicted probabilities. Plots were generated separately by sex for all patients and for subgroups of age and CCI based on summary statistics pooled across the imputed data sets. When examining calibration, we estimated observed risk for censored data in two ways: (1) using the standard Kaplan–Meier estimator (which is consistent with the assumptions made in QFracture-2012 derivation in that it ignores competing risks) and (2) using the Aalen–Johansen estimator (an extension to allow for competing events, non-fracture death in this case).[84] All models were fitted in R and Stata.

Analytical methods: competing risk model derivation and internal validation

Competing risk model derivation and internal validation was carried out in the same data set as QFracture-2012 external validation. For this purpose, participants were randomly allocated to distinct derivation and test data sets in a 2 : 1 ratio, with allocation balanced in terms of age and final event status. The derivation data set was used to derive CFracture, a Fine–Gray model to predict the 10-year risk of experiencing a CVD event, accounting for the competing risk of non-CVD death. Separate models were estimated for men and women. Reflecting the overall aim of the project where we wished to explicitly compare prediction in models accounting for competing risk compared with ignoring competing risk, we included all the same main effects (predictors) and age interactions as QFracture-2012 modified, as follows. we accounted for non-fracture death as a second (competing)

outcome using the Fine–Gray model and we additionally included the CCI score in the model (categorised as 0, 1, 2 or ≥ 3), as CCI is a well-validated predictor of total mortality.[12] Fine–Gray models allow the cumulative incidence function or probability of a CVD event occurring over time to be directly predicted, but the subdistribution HRs in the Fine–Gray models do not have a straightforward interpretation, as they describe the direction but not the magnitude of the effect of predictors on the cumulative incidence function. The use of fractional polynomials and the inclusion of complex interactions with age further complicate direct interpretation of model coefficients. Model coefficients are, therefore, not straightforwardly interpretable, but the derived model is provided in *Appendix 4*, *Tables 38–41*, to allow replication.

The performance of CFracture and QFracture-2012 was evaluated in the independent validation data set by examining discrimination and calibration, as described above. R 4.0.0 was used for all analyses.

Results 1: external validation of QFracture-2012 for major osteoporotic fracture

There were 2,747,409 women and 2,684,730 men included in the external validation data set, with a mean age of 50.7 years in women and 48.5 years in men (vs. 50 years in the QFracture-2012 internal validation cohort[26]) (see *Appendix 4*, *Table 42*). Compared with the QFracture-2012 internal validation cohort, there were more people with a history of MOF at baseline (5.5% of women and 4.2% of men, vs. 1.8% of all participants in QFracture-2012), type 2 diabetes (3.0% of women and 3.7% of men vs. 2.7% of all participants in QFracture-2012), history of falls (5.6% of women and 2.8% of men vs. 1.1% of all participants in QFracture-2012), cancer (3.4% of women and 2.5% of men vs. 1.8% of all participants in QFracture-2012), asthma or chronic obstructive pulmonary disease (12.9% of women and 11.3% of men vs. 7.1% of all participants in QFracture-2012) and chronic renal disease (1.2% of women and 0.9% of men vs. 0.2% of all participants in QFracture-2012). Compared with the QFracture-2012 internal validation cohort, there was a higher proportion of missing data for BMI and smoking status, but fewer missing data for ethnicity. Fracture rates rose steadily with age; however, competing mortality rates rose faster, and in patients aged 90–99 years mortality rates were between five (women) and 10 (men) times the MOF rate (see *Appendix 4*, *Figure 32*).

In women, during 15,624,543 years of follow-up, there were 95,598 incident cases of MOF observed [6.12 (95% CI 6.08 to 6.16) cases per 1000 person-years]. In men, during 15,179,623 years of follow-up, there were 34,321 incident cases of MOF [2.26 (95% CI 2.24 to 2.29) cases per 1000 person-years]. Compared with the previous QFracture-2012 external validation,[18] our observed crude incidence of MOF was substantially higher (women, 6.12/1000 person-years vs. 2.93; men, 2.26/1000 person-years vs. 0.98) (see *Appendix 4*, *Table 43*). However, the previous study was restricted to patients aged 30–84 years, and differences were smaller but still substantial. Restricting incidence estimation in this study to this population resulted in 5.33 cases per 1000 person-years for women (vs. 2.08) and 226 cases per 1000 person-years for men (vs. 0.98).

To explore the effect of including hospital ascertainment of fracture using HES admitted patient care, we also estimated fracture rates using only GP and mortality data (as was carried out in QFracture-2012 derivation and validation),[18,26] and this accounted for only a minority of the additional observed MOFs in this study (see *Appendix 4*, *Figure 33*).

Discrimination of QFracture-2012 for MOF in the whole external validation population was excellent in women (with a Harrell's *c*-statistic of 0.813 vs. an AUROC of 0.790 in QFracture-2012 internal validation) and good in men (with a Harrell's *c*-statistic of 0.738 vs. an AUROC of 0.711 in QFracture-2012 internal validation) (*Table 6*). The D-statistic was 2.25 in women and 1.76 in men, similar but somewhat better than in QFracture-2012 internal validation (2.13 and 1.61, respectively). The model explained 54.8% of variation in outcome in women and 42.4% of variation in outcome in men,

TABLE 6 Discrimination of the QFracture-2012 model for MOF

Patient group	Women			Men		
	Harrell's *c*-statistic (95% CI)	D-statistic (95% CI)	R^2-statistic (95% CI)	Harrell's *c*-statistic (95% CI)	D-statistic (95% CI)	R^2-statistic (95% CI)
All patients	0.813 (0.811 to 0.815)	2.25 (2.24 to 2.27)	54.8 (54.5 to 55.1)	0.738 (0.735 to 0.741)	1.76 (1.74 to 1.78)	42.4 (41.9 to 43.0)
Age group (years)						
30–64	0.709 (0.706 to 0.712)	1.30 (1.28 to 1.32)	28.8 (28.2 to 29.4)	0.625 (0.621 to 0.630)	0.84 (0.81 to 0.86)	14.4 (13.6 to 15.1)
65–74	0.616 (0.612 to 0.620)	0.71 (0.69 to 0.73)	10.7 (10.1 to 11.4)	0.660 (0.653 to 0.668)	1.00 (0.95 to 1.04)	19.2 (17.9 to 20.6)
75–84	0.615 (0.612 to 0.619)	0.67 (0.65 to 0.69)	9.6 (9.1 to 10.2)	0.652 (0.645 to 0.659)	0.91 (0.87 to 0.95)	16.4 (15.2 to 17.6)
85–99	0.576 (0.570 to 0.581)	0.38 (0.35 to 0.42)	3.4 (2.9 to 4.0)	0.624 (0.613 to 0.636)	0.67 (0.60 to 0.73)	9.6 (8.0 to 11.3)
mCCI						
0	0.795 (0.793 to 0.798)	2.08 (2.06 to 2.10)	50.8 (50.4 to 51.2)	0.668 (0.664 to 0.673)	1.22 (1.20 to 1.25)	26.3 (25.4 to 27.1)
1	0.801 (0.797 to 0.805)	2.08 (2.05 to 2.10)	50.7 (50.1 to 51.4)	0.730 (0.723 to 0.737)	1.64 (1.59 to 1.68)	39.0 (37.7 to 40.2)
2	0.747 (0.742 to 0.753)	1.60 (1.56 to 1.63)	37.8 (36.9 to 38.8)	0.727 (0.719 to 0.736)	1.54 (1.49 to 1.60)	36.3 (34.6 to 37.9)
≥ 3	0.712 (0.706 to 0.718)	1.30 (1.26 to 1.33)	28.7 (27.5 to 29.8)	0.724 (0.715 to 0.733)	1.46 (1.40 to 1.51)	33.7 (32.0 to 35.4)

Source: Livingstone *et al.*[50]

compared with 51.9% and 38.2%, respectively, in QFracture-2012 internal validation. Stratified by age, discrimination in women was good (Harrell's *c*-statistic 0.756 for women aged 85–99 years) to moderate (Harrell's *c*-statistic 0.709 for women aged 30–64 years), and moderate in all ages in men. Explained variation was lower in all strata and low in those aged 85–99 years (women, 3.4%; men, 9.6%). Stratified by CCI, discrimination was good at all levels of comorbidity.

Ignoring competing mortality risk in the estimation of observed risk of MOF (*Figures 7* and *8*, parts a, c and e), there was underprediction at all levels of predicted risk for both men and women, which was larger at higher levels of predicted risk (see *Figures 7* and *8*, part a). Stratified by age, there was underprediction in all age groups. Underprediction was larger in older people, although there was overprediction in 85- to 99-year-olds at highest levels of predicted risk (see *Figures 7* and *8*, part b). Stratified by CCI, there was underprediction at all levels of comorbidity. Underprediction was largest in people with a CCI score ≥ 3, although there was overprediction at the highest levels of predicted risk (see *Figures 7* and *8*, part c).

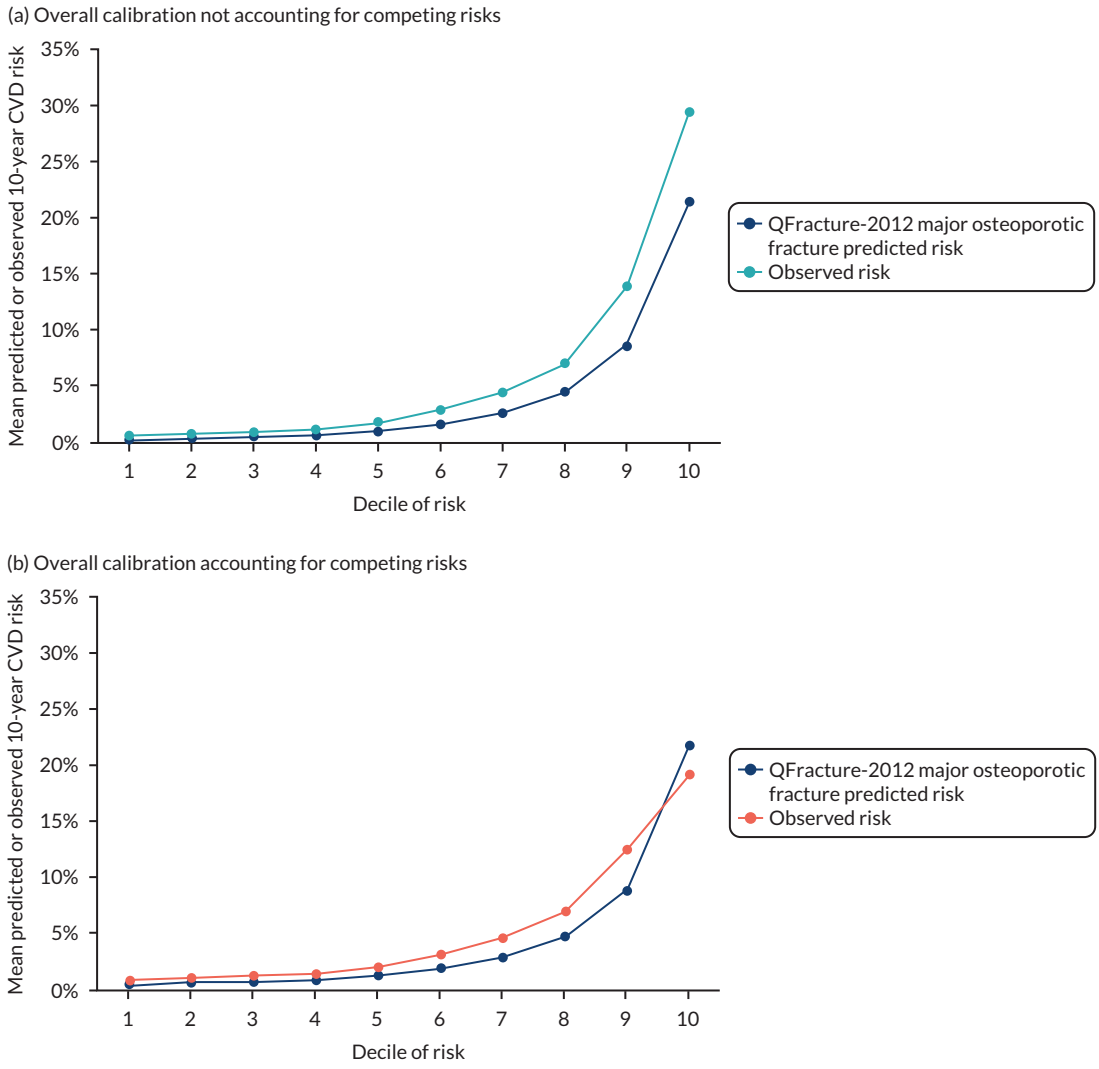
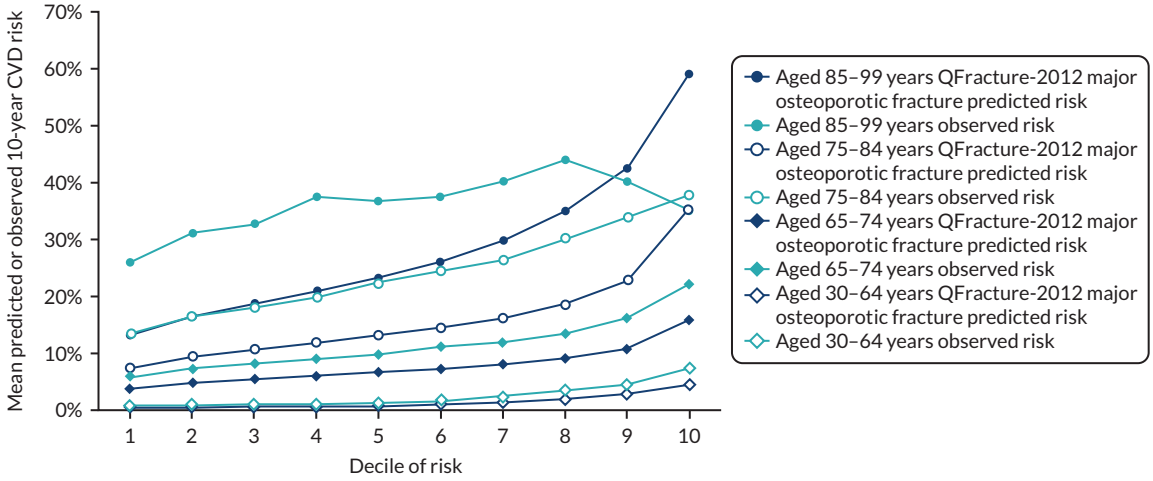
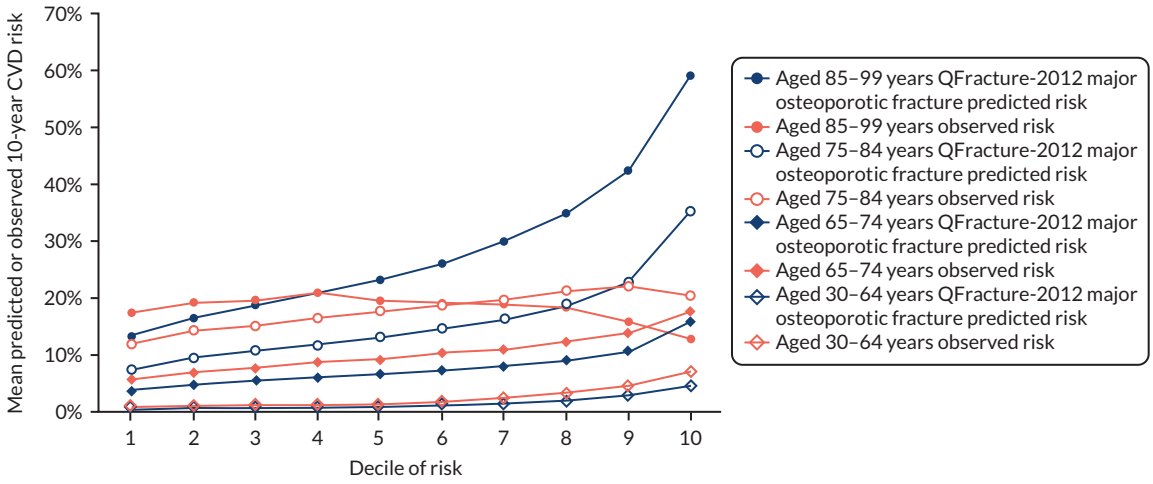


FIGURE 7 Calibration for MOF in women without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. A coloured line (i.e. observed risk) above the matching black line (i.e. predicted risk) indicates underprediction. A coloured line (i.e. observed risk) below the matching black line (i.e. predicted risk) indicates overprediction. Source: Livingstone *et al.*[50] (*continued*)

(c) Calibration by age group not accounting for competing risks



(d) Calibration by age group accounting for competing risks



(e) Calibration by CCI not accounting for competing risks

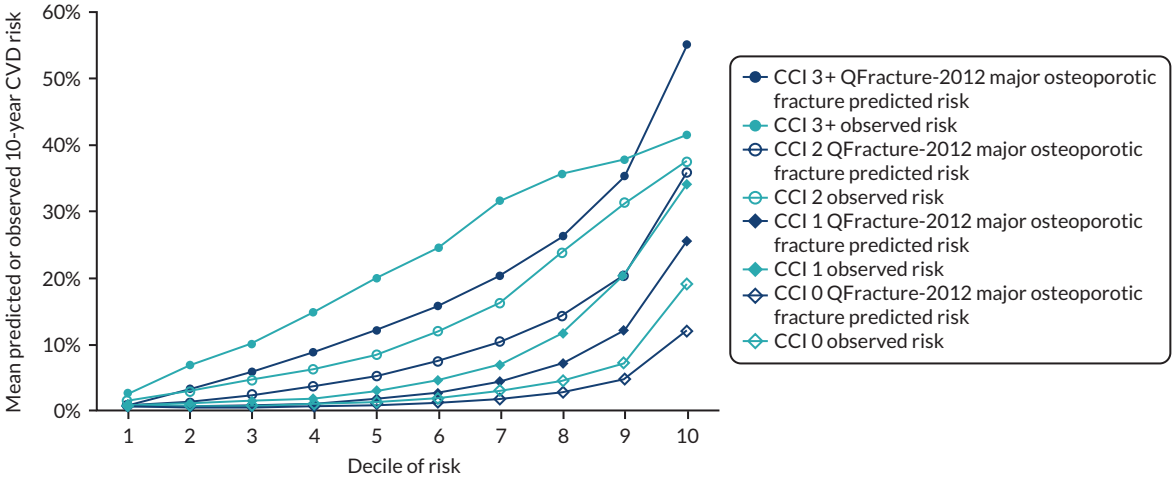


FIGURE 7 Calibration for MOF in women without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. A coloured line (i.e. observed risk) above the matching black line (i.e. predicted risk) indicates underprediction. A coloured line (i.e. observed risk) below the matching black line (i.e. predicted risk) indicates overprediction. Source: Livingstone *et al.*[50] (*continued*)

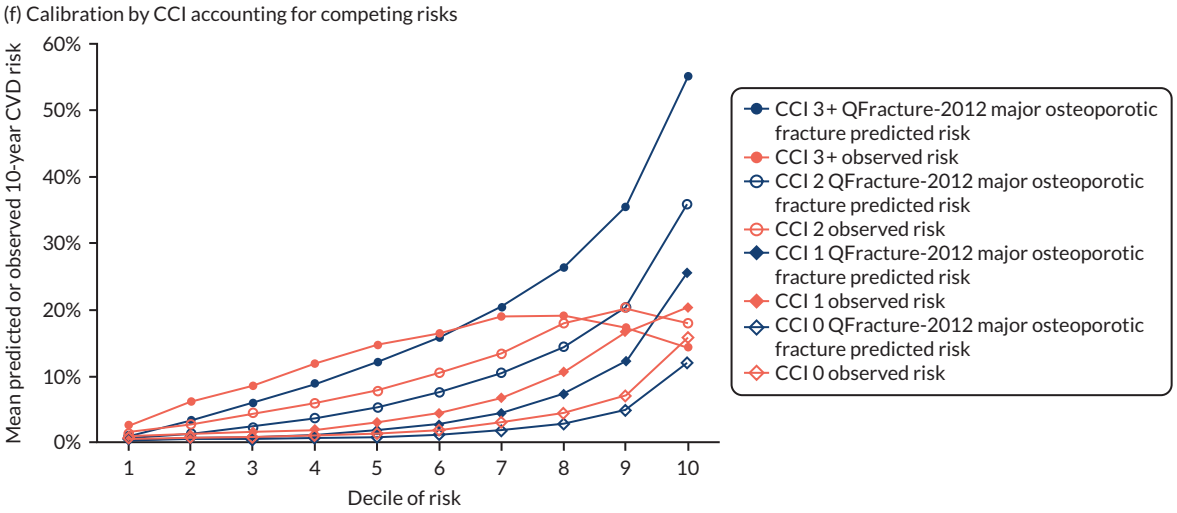


FIGURE 7 Calibration for MOF in women without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. A coloured line (i.e. observed risk) above the matching black line (i.e. predicted risk) indicates underprediction. A coloured line (i.e. observed risk) below the matching black line (i.e. predicted risk) indicates overprediction. Source: Livingstone *et al.*[50]

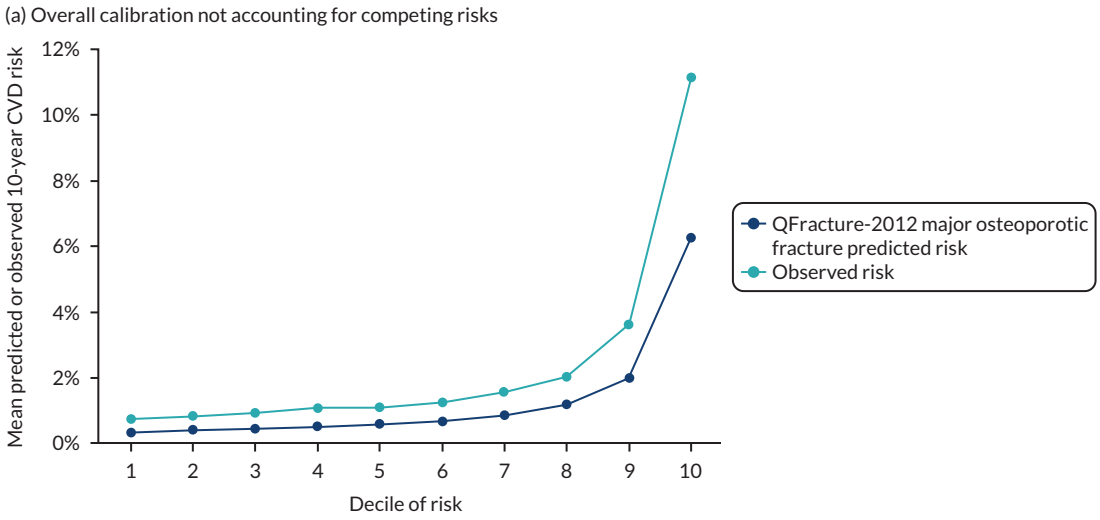


FIGURE 8 Calibration for MOF in men without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. A coloured line (i.e. observed risk) below the matching black line (i.e. predicted risk) indicates overprediction. Source: Livingstone *et al.*[50] (*continued*)

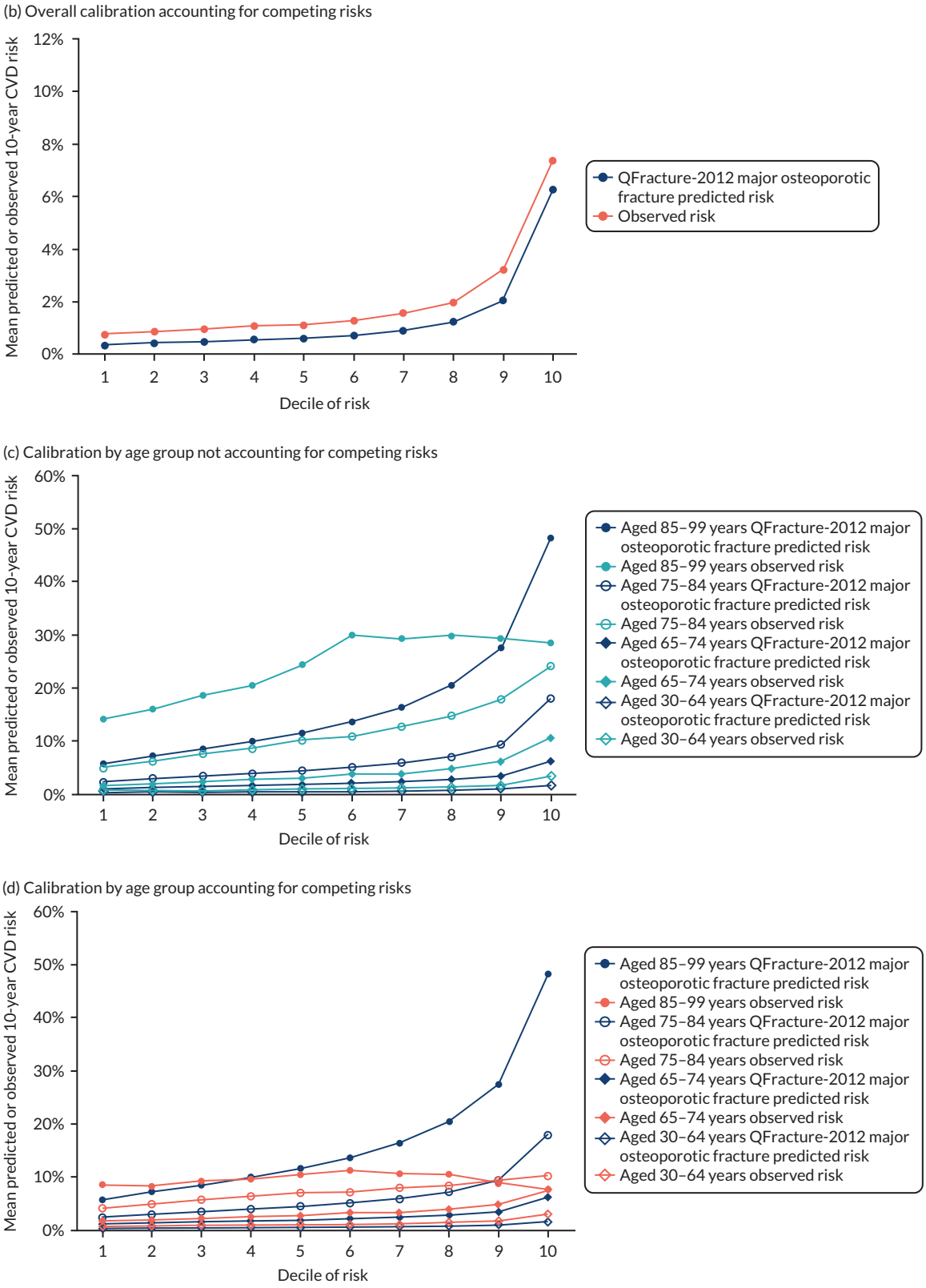


FIGURE 8 Calibration for MOF in men without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. A coloured line (i.e. observed risk) below the matching black line (i.e. predicted risk) indicates overprediction. Source: Livingstone *et al.*[50] *(continued)*

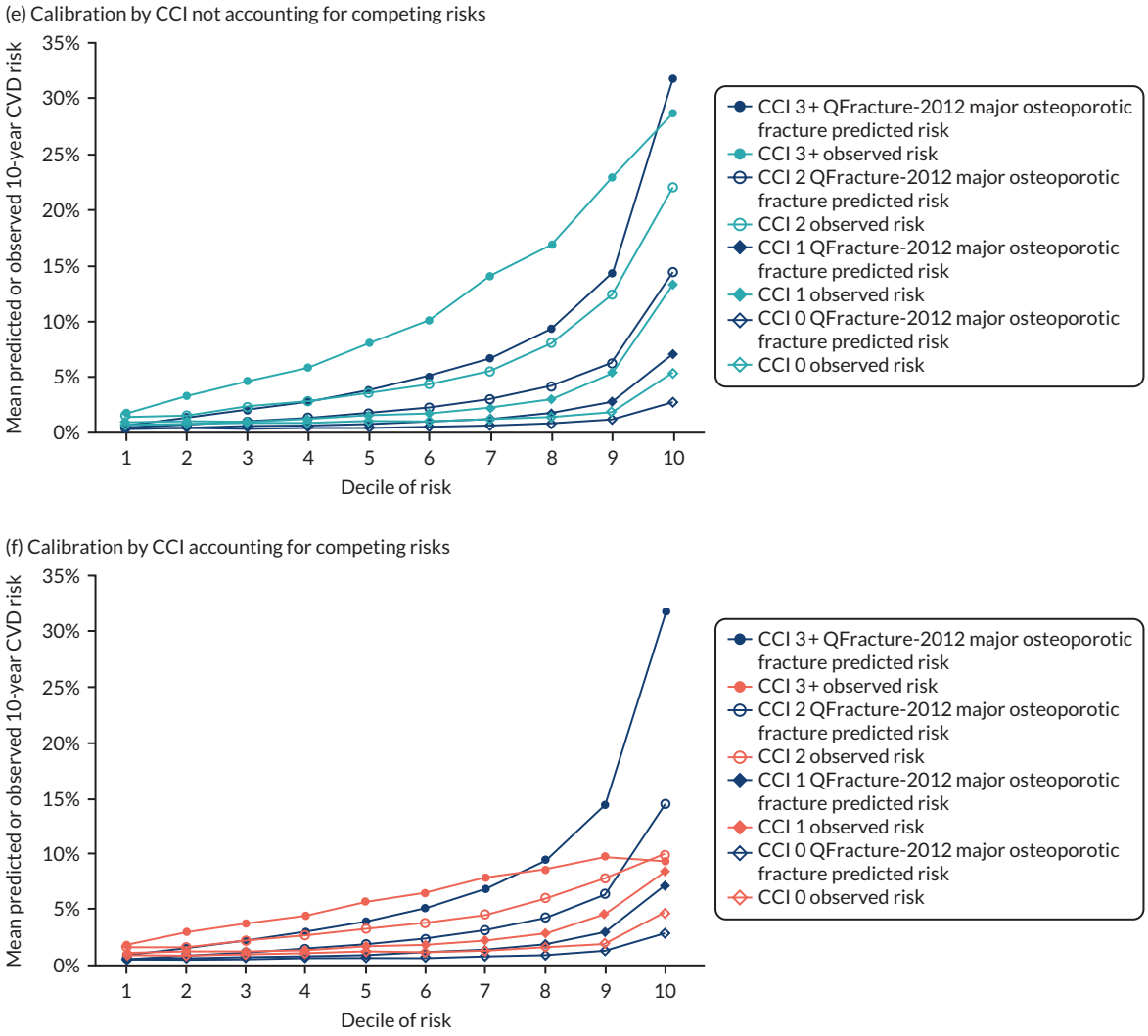


FIGURE 8 Calibration for MOF in men without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. A coloured line (i.e. observed risk) below the matching black line (i.e. predicted risk) indicates overprediction. Source: Livingstone *et al.*[50]

Accounting for competing mortality risk in the estimation of observed risk of MOF (see *Figures 7* and *8*, parts b, d and f), there was still underprediction in the whole population, but less than observed when ignoring competing mortality. Stratified by age, there was underprediction in both men and women aged 30–64 years and 65–74 years (see *Figures 7* and *8*, parts d and e). In the older-age groups, there was underprediction at lower levels of predicted risk, but overprediction at higher levels of predicted risk. Notably, in both women and men aged 85–99 years, observed risk accounting for competing mortality declined across the 10 deciles of increasing predicted risk. Similar patterns were observed stratified by CCI, with underprediction in people with low comorbidity, but large overprediction in people with a CCI score ≥ 3 at higher levels of predicted risk (see *Figures 7* and *8*, part f).

Results 2: external validation of QFracture-2012 for hip fracture

In women, during 15,842,775 years of follow-up, there were 36,400 incident cases of hip fracture observed [2.30 (95% CI 2.27 to 2.32) cases per 1000 person-years]. In men, during 15,253,462 years

of follow-up, there were 13,379 incident cases of hip fracture [0.88 (95% CI 0.86 to 0.89) cases per 1000 person-years]. Compared with the previous QFracture-2012 external validation,[18] observed crude incidence of hip fracture was substantially higher (women, 2.30/1000 person-years vs. 1.37; men, 0.88/1000 person-years vs. 0.47). However, the previous study was restricted to people aged 30–84 years, and differences were smaller but still substantial. Restricting incidence estimation in this study to this population resulted in 1.73 cases per 1000 person-years for women (vs. 1.37) 0.74 cases per 1000 person-years for men (vs. 0.47). Ignoring hip fractures ascertained in hospital coding accounted for all the difference in incidence in women, and for most of the difference in men (see *Appendix 4*, *Figure 33*).

Discrimination of QFracture-2012 for hip fracture in the whole external validation population was excellent in women (with a Harrell's *c*-statistic of 0.918 vs. an AUROC of 0.893 in QFracture-2012 internal validation) and good in men (with a Harrell's *c*-statistic of 0.888 vs. an AUROC of 0.875 in QFracture-2012 internal validation) (*Table 7*). The D-statistic was 3.26 in women and 3.19 in men, which is very similar to QFracture-2012 internal validation (3.26 and 3.15, respectively). The model explained 71.7% of variation in outcome in women and 70.9% of variation in outcome in men, which is very similar to QFracture-2012 internal validation (71.7% and 70.4%, respectively). Stratified by age, discrimination in women was moderate (Harrell's *c*-statistic 0.601 for women aged 85–99 years) to excellent (Harrell's *c*-statistic 0.832 for women aged 30–64 years), and moderate (Harrell's *c*-statistic 0.637 for men aged 85–99 years) to good (Harrell's *c*-statistic 0.765 for men aged 30–64 years) in men. Explained variation was lower in all strata and low in those people aged 85–99 years (women, 5.8%; men, 11.8%). Stratified by CCI, discrimination was good to excellent at all levels of comorbidity.

Ignoring competing mortality risk in the estimation of observed risk of hip fracture (*Figures 9* and *10*, parts a, c and e), there was underprediction at all levels of predicted risk for both men and women, which was larger at higher levels of predicted risk (see *Figures 9* and *10*, part a) and larger than for MOF. Stratified by age, there was underprediction in all age groups. Underprediction was larger in older people, although there was overprediction in 85- to 99-year-olds at highest levels of predicted risk (see *Figures 9* and *10*, part b). Stratified by CCI, there was underprediction at all levels of comorbidity. Underprediction was largest in people with a CCI score ≥ 3, although there was overprediction at the highest levels of predicted risk (see *Figures 9* and *10*, part c).

Accounting for competing mortality risk in the estimation of observed risk of hip fracture (see *Figures 9* and *10*, parts b, d and f), there was still underprediction in the whole population, but less than observed when ignoring competing mortality. Stratified by age, there was underprediction in all deciles of predicted risk in women aged 30–64 years and men aged 30–64 years and 65–74 years (see *Figures 9* and *10*, parts d and e). In the older age groups, there was underprediction at lower levels of predicted risk, but overprediction at higher levels of predicted risk. Notably, in both women and men aged 74–85 years and 85–99 years, observed risk accounting for competing mortality was flat or declined slightly across the 10 deciles of increasing predicted risk. Similar patterns were observed when stratified by CCI, with underprediction in people with low comorbidity, but large overprediction in people with a CCI score ≥ 3 at higher levels of predicted risk (see *Figures 9* and *10*, part f).

Results 3: derivation and internal validation of CFracture

There were 1,831,606 women and 1,789,820 men aged 30–99 years in the derivation cohort, and 915,803 and 894,910, respectively, in the validation cohort, with similar distribution of baseline characteristics in each. Two new CFracture models were created for MOF and for hip fracture, both using the same variables as QFracture-2012 but accounting for competing mortality risk in derivation and including baseline CCI in prediction.

TABLE 7 Discrimination of the QFracture-2012 model for hip fracture

	Women			Men		
Patient group	**Harrell's *c*-statistic (95% CI)**	**D-statistic (95% CI)**	**R^2-statistic (95% CI)**	**Harrell's *c*-statistic (95% CI)**	**D-statistic (95% CI)**	**R^2-statistic (95% CI)**
All patients	0.918 (0.915 to 0.921)	3.26 (3.24 to 3.28)	71.7 (71.4 to 71.9)	0.888 (0.882 to 0.893)	3.19 (3.16 to 3.23)	70.9 (70.4 to 71.3)
Age group (years)						
30–64	0.832 (0.823 to 0.841)	2.24 (2.19 to 2.30)	54.6 (53.4 to 55.8)	0.765 (0.755 to 0.776)	1.88 (1.82 to 1.94)	45.8 (44.1 to 47.4)
65–74	0.694 (0.687 to 0.701)	1.20 (1.16 to 1.24)	25.7 (24.4 to 27.0)	0.705 (0.694 to 0.716)	1.29 (1.23 to 1.36)	28.5 (26.5 to 30.5)
75–84	0.664 (0.659 to 0.669)	0.95 (0.92 to 0.98)	17.7 (16.8 to 18.5)	0.679 (0.670 to 0.687)	1.08 (1.03 to 1.13)	21.7 (20.1 to 23.3)
85–99	0.601 (0.595 to 0.608)	0.51 (0.47 to 0.55)	5.8 (5.0 to 6.7)	0.637 (0.623 to 0.651)	0.75 (0.67 to 0.82)	11.8 (9.8 to 13.9)
CCI						
0	0.924 (0.919 to 0.929)	3.36 (3.33 to 3.39)	72.9 (72.6 to 73.3)	0.852 (0.844 to 0.860)	2.84 (2.79 to 2.89)	65.8 (64.9 to 66.6)
1	0.899 (0.893 to 0.905)	2.92 (2.88 to 2.96)	67.1 (66.4 to 67.7)	0.872 (0.861 to 0.882)	2.89 (2.82 to 2.96)	66.7 (65.6 to 67.7)
2	0.839 (0.831 to 0.846)	2.24 (2.19 to 2.29)	54.5 (53.4 to 55.5)	0.808 (0.796 to 0.821)	2.17 (2.09 to 2.25)	53.0 (51.1 to 54.7)
≥ 3	0.783 (0.775 to 0.792)	1.75 (1.70 to 1.80)	42.2 (40.8 to 43.5)	0.782 (0.770 to 0.794)	1.90 (1.83 to 1.97)	46.4 (44.5 to 48.2)

Source: Livingstone *et al.*[50]

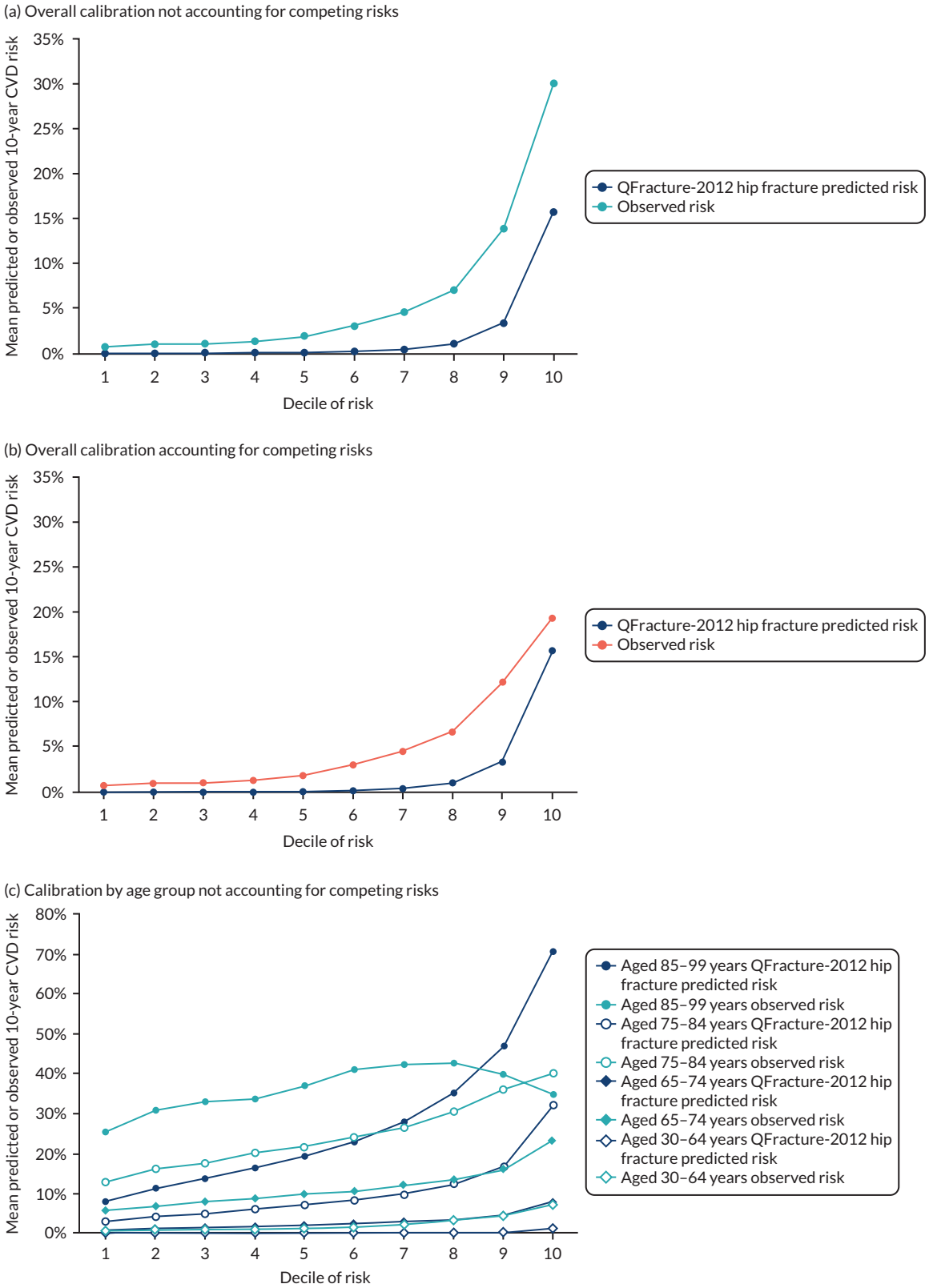


FIGURE 9 Calibration for hip fracture in women without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. A coloured line (i.e. observed risk) above the matching black line (i.e. predicted risk) indicates underprediction. A coloured line (i.e. observed risk) below the matching black line (i.e. predicted risk) indicates overprediction. Source: Livingstone *et al.*[50] (*continued*)

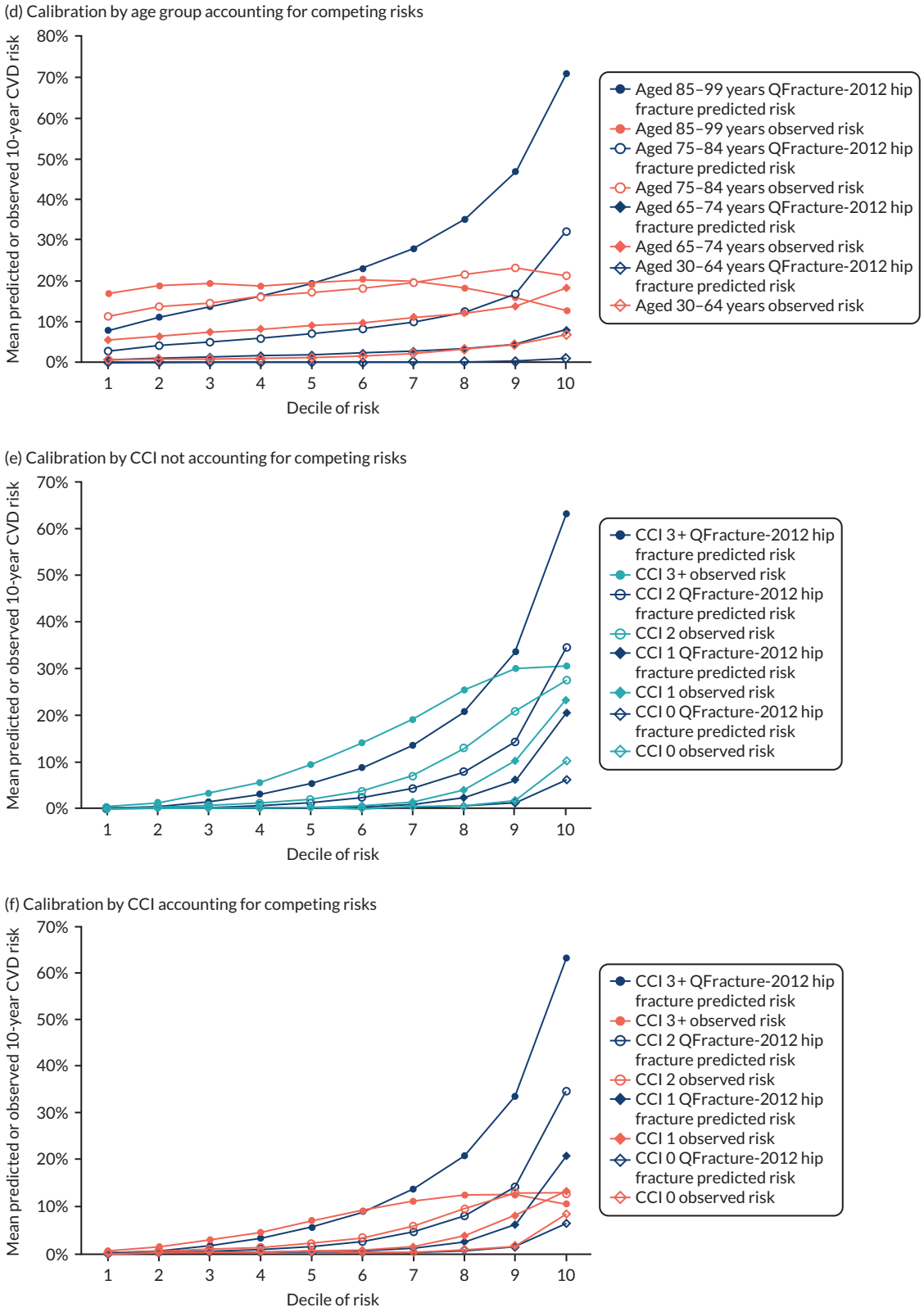


FIGURE 9 Calibration for hip fracture in women without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. A coloured line (i.e. observed risk) above the matching black line (i.e. predicted risk) indicates underprediction. A coloured line (i.e. observed risk) below the matching black line (i.e. predicted risk) indicates overprediction. Source: Livingstone *et al.*[50]

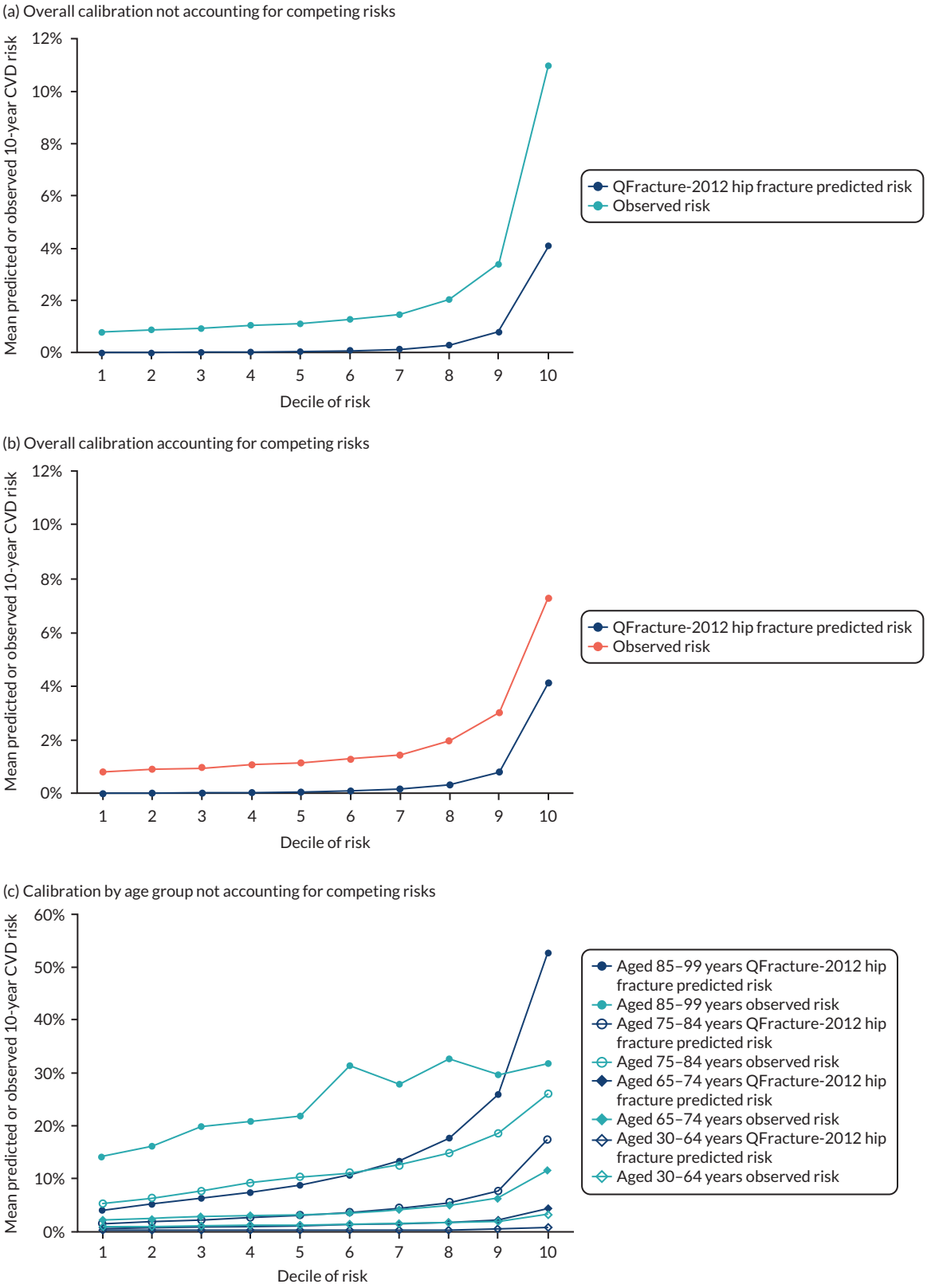


FIGURE 10 Calibration for hip fracture in men without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. A coloured line (i.e. observed risk) above the matching black line (i.e. predicted risk) indicates underprediction. A coloured line (i.e. observed risk) below the matching black line (i.e. predicted risk) indicates overprediction. Source: Livingstone *et al.*[50] (*continued*)

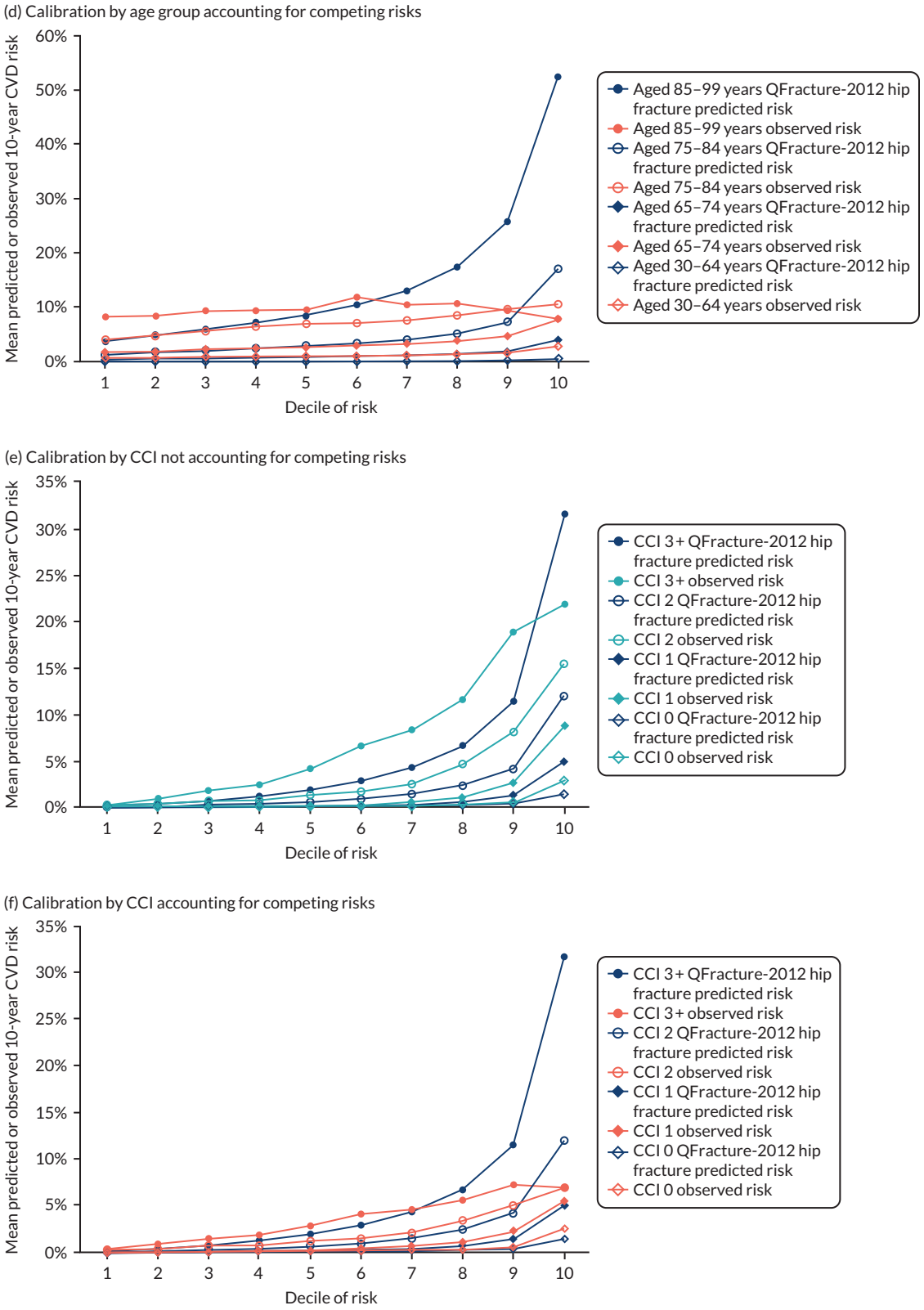


FIGURE 10 Calibration for hip fracture in men without accounting for competing risks and accounting for competing risks. (a) Overall calibration not accounting for competing risks;[a] (b) overall calibration accounting for competing risks;[b] (c) calibration by age group not accounting for competing risks;[a] (d) calibration by age group accounting for competing risks;[b] (e) calibration by CCI not accounting for competing risks;[a] and (f) calibration by CCI accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. A coloured line (i.e. observed risk) above the matching black line (i.e. predicted risk) indicates underprediction. A coloured line (i.e. observed risk) below the matching black line (i.e. predicted risk) indicates overprediction. Source: Livingstone *et al.*[50]

Performance of CFracture for predicting major osteoporotic fracture

In the internal validation cohort, discrimination of CFracture for MOF in the whole population was excellent in women (Harrell's *c*-statistic 0.813, 95% CI 0.810 to 0.816) and good in men (Harrell's *c*-statistic 0.738, 95% CI 0.732 to 0.743), which is similar to QFracture-2012 for MOF in the same cohort (*Table 8*). Stratified by age, discrimination of both CFracture and QFracture-2012 was lower in all age groups and declined with age in women, although was similar in all age groups in men. Stratified by comorbidity, discrimination in the strata was somewhat worse than in the whole population, but there was no clear pattern of change with increasing comorbidity.

Calibration of CFracture for MOF was better than for QFracture-2012 in the whole population. In women, there was some underprediction at higher levels of predicted risk and a in men there was a similar calibration, but with some overprediction in the middle range of predicted risk (*Figure 11*). Stratified by age, calibration was good in women aged 30–64 years, with some underprediction in women aged 65–74 years and 75–84 years (*Figure 12*). In men, there was some overprediction a higher levels of predicted risk in those aged 30–64 years and 75–84 years, and some overprediction in those aged 65–74 years. In both men and women aged 85–99 years, calibration was poor, although considerably better than QFracture-2012 in this age group, as well as all others. Stratified by CCI, calibration in women was good, although with some underprediction in women with a CCI score of 0 and some overprediction in women with a CCI score ≥ 3 in the highest decile of predicted risk (*Figure 13*). Calibration in men stratified by CCI was more variable in those with a CCI score of 0 or 1 but was good in those with a CCI score of 2 and in those with a CCI score ≥ 3, for whom it was good apart from some overprediction in the decile of highest predicted risk.

Performance of CFracture for predicting hip fracture

In the internal validation cohort, discrimination of CFracture for hip fracture in the whole population was excellent in both women (Harrell's *c*-statistic 0.914, 95% CI 0.908 to 0.883) and men (Harrell's *c*-statistic 0.886, 95% CI 0.877 to 0.895), similar to QFracture-2012 for hip fracture in the same cohort (*Table 9*). Stratified by age, discrimination of both CFracture and QFracture-2012 was lower in all age groups and declined with age in both men and women. Stratified by comorbidity, discrimination was good to excellent in all strata, although declined with increasing comorbidity.

TABLE 8 Discrimination of CFracture and QFracture-2012 for MOF in women and men in the validation cohort

	Women		Men	
Patient group	**CFracture, Harrell's *c*-statistic (95% CI)**	**QFracture-2012, Harrell's *c*-statistic (95% CI)**	**CFracture, Harrell's *c*-statistic (95% CI)**	**QFracture-2012, Harrell's *c*-statistic (95% CI)**
All patients	0.813 (0.810 to 0.816)	0.813 (0.810 to 0.817)	0.738 (0.732 to 0.743)	0.736 (0.730 to 0.741)
Age group (years)				
30–64	0.711 (0.705 to 0.717)	0.709 (0.703 to 0.715)	0.623 (0.615 to 0.631)	0.619 (0.611 to 0.627)
65–74	0.620 (0.613 to 0.627)	0.614 (0.607 to 0.621)	0.653 (0.640 to 0.666)	0.653 (0.641 to 0.666)
75–84	0.610 (0.604 to 0.617)	0.617 (0.610 to 0.623)	0.640 (0.629 to 0.652)	0.646 (0.635 to 0.658)
85–99	0.564 (0.555 to 0.574)	0.568 (0.558 to 0.577)	0.618 (0.598 to 0.639)	0.623 (0.602 to 0.643)
CCI				
0	0.797 (0.792 to 0.801)	0.795 (0.791 to 0.800)	0.665 (0.657 to 0.673)	0.665 (0.657 to 0.673)
1	0.801 (0.794 to 0.808)	0.802 (0.796 to 0.809)	0.725 (0.714 to 0.737)	0.725 (0.714 to 0.737)
2	0.754 (0.745 to 0.763)	0.753 (0.744 to 0.762)	0.730 (0.714 to 0.745)	0.730 (0.714 to 0.745)
≥ 3	0.701 (0.690 to 0.711)	0.711 (0.701 to 0.721)	0.714 (0.698 to 0.730)	0.714 (0.698 to 0.730)

Source: Livingstone *et al.*[51]

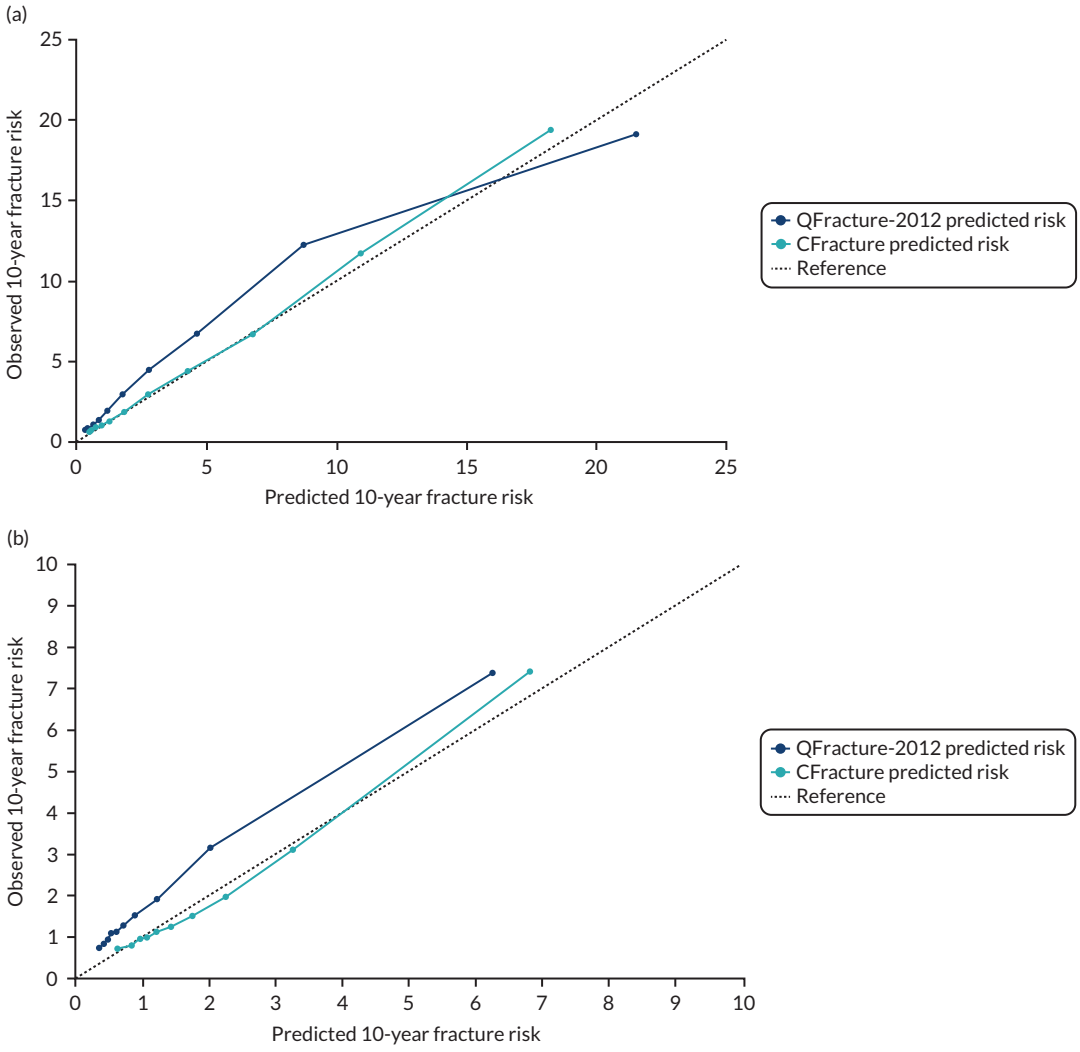


FIGURE 11 Whole-population calibration of CFracture and QFracture-2012 for MOF in the internal validation data set in the whole population. (a) Women; and (b) men. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Source: Livingstone *et al.*[51]

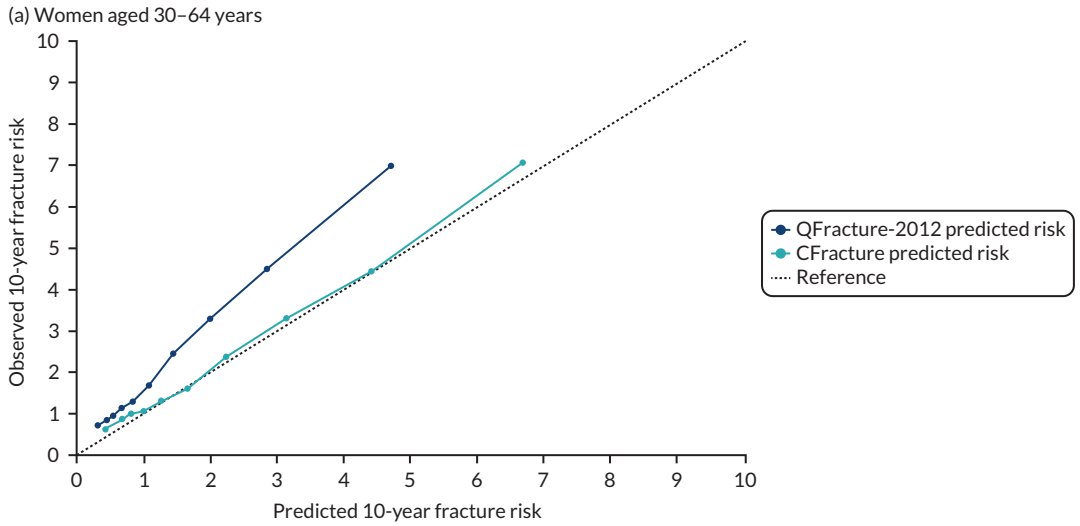


FIGURE 12 Calibration of CFracture and QFracture-2012 for MOF in the internal validation data set stratified by age group. (a) Women aged 30–64 years; (b) men aged 30–64 years; (c) women aged 65–74 years; (d) men aged 65–74 years; (e) women aged 75–84 years; (f) men aged 75–84 years; (g) women aged 85–99 years; and (h) men aged 85–99 years. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line. Below the reference line is overprediction and above the reference line is underprediction. Source: Livingstone *et al.*[51] (*continued*)

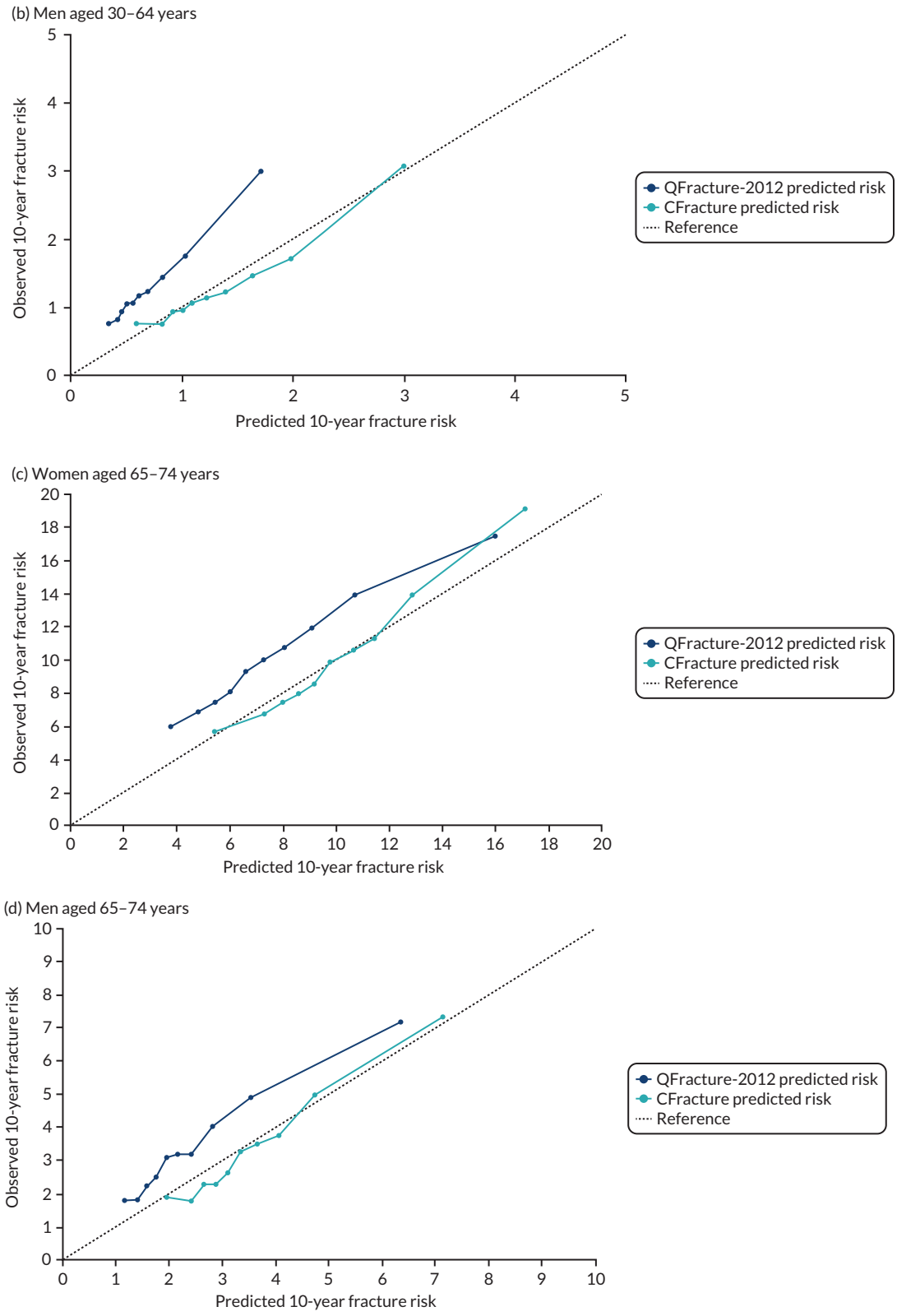


FIGURE 12 Calibration of CFracture and QFracture-2012 for MOF in the internal validation data set stratified by age group. (a) Women aged 30–64 years; (b) men aged 30–64 years; (c) women aged 65–74 years; (d) men aged 65–74 years; (e) women aged 75–84 years; (f) men aged 75–84 years; (g) women aged 85–99 years; and (h) men aged 85–99 years. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line. Below the reference line is overprediction and above the reference line is underprediction. Source: Livingstone *et al.*[51] (*continued*)

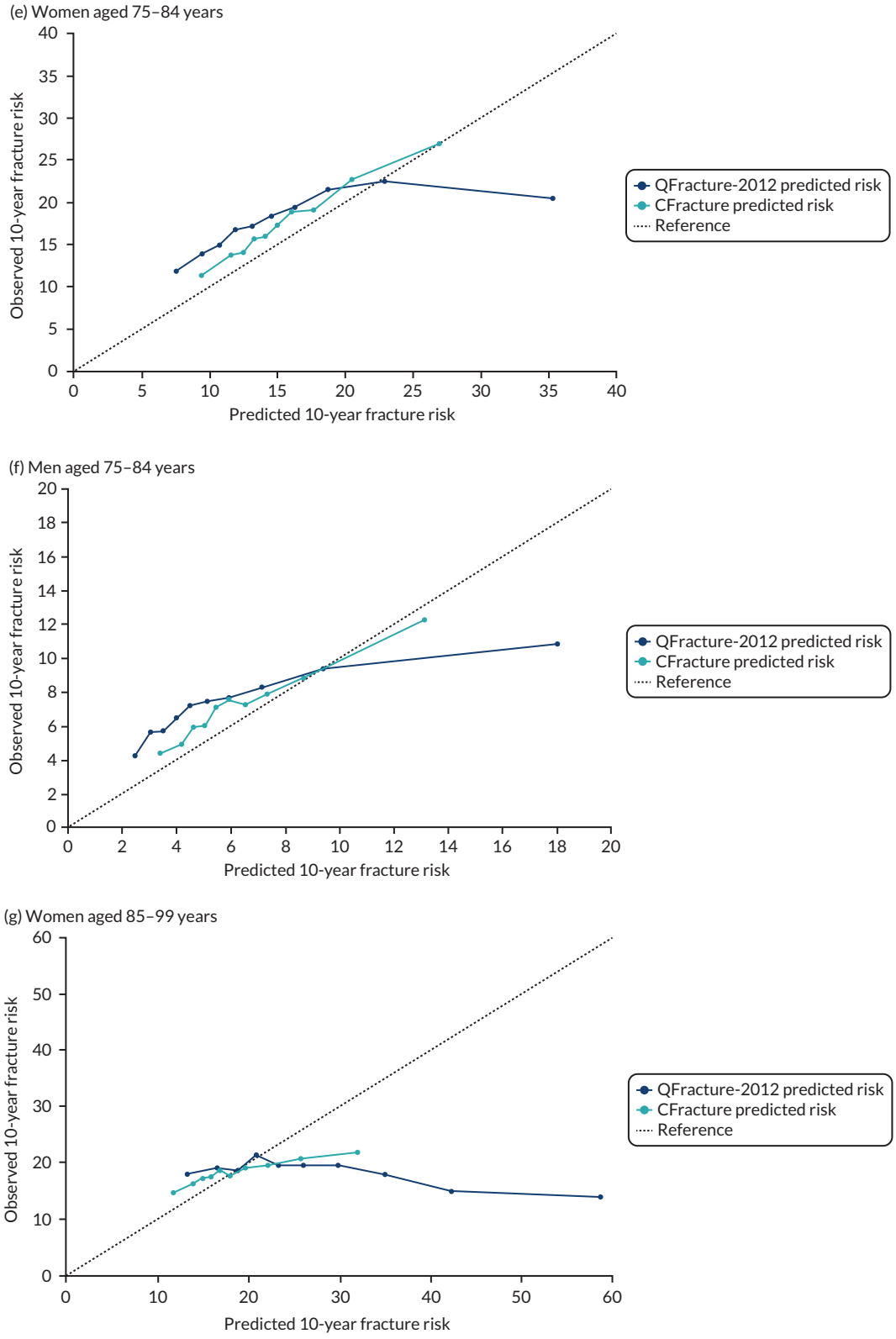


FIGURE 12 Calibration of CFracture and QFracture-2012 for MOF in the internal validation data set stratified by age group. (a) Women aged 30–64 years; (b) men aged 30–64 years; (c) women aged 65–74 years; (d) men aged 65–74 years; (e) women aged 75–84 years; (f) men aged 75–84 years; (g) women aged 85–99 years; and (h) men aged 85–99 years. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line. Below the reference line is overprediction and above the reference line is underprediction. Source: Livingstone *et al.*[51] (*continued*)

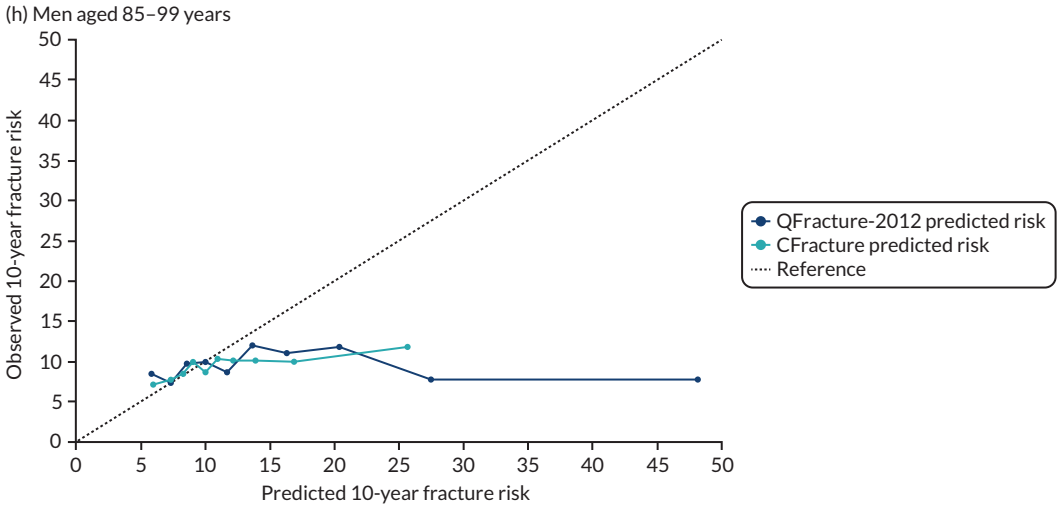


FIGURE 12 Calibration of CFracture and QFracture-2012 for MOF in the internal validation data set stratified by age group. (a) Women aged 30–64 years; (b) men aged 30–64 years; (c) women aged 65–74 years; (d) men aged 65–74 years; (e) women aged 75–84 years; (f) men aged 75–84 years; (g) women aged 85–99 years; and (h) men aged 85–99 years. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line. Below the reference line is overprediction and above the reference line is underprediction. Source: Livingstone *et al.*[51]

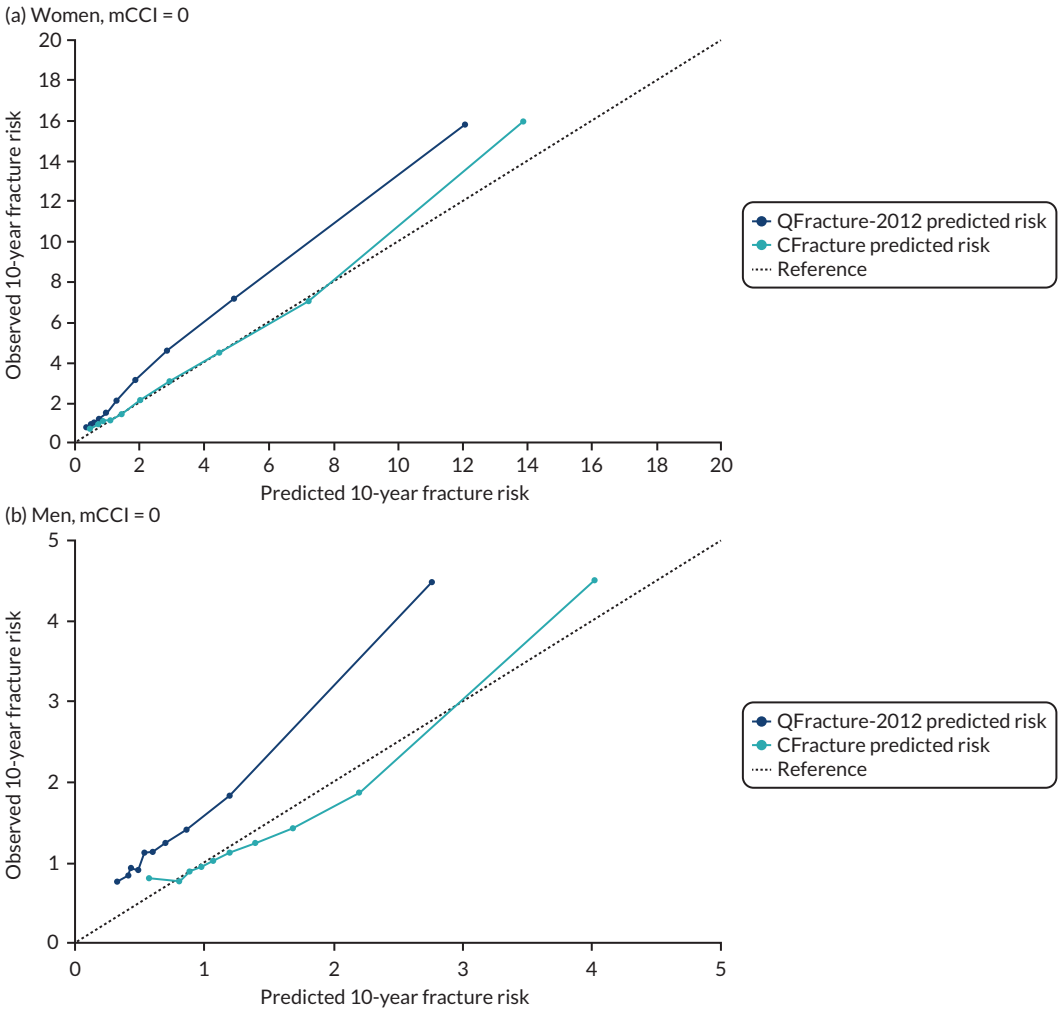


FIGURE 13 Calibration of CFracture and QFracture-2012 for MOF in the internal validation data set stratified by mCCI. (a) Women, mCCI = 0; (b) men, mCCI = 0; (c) women mCCI = 1; (d) men, mCCI = 1; (e) women, mCCI = 2; (f) men, mCCI = 2; (g) women, mCCI ≥ 3; and (h) men, mCCI ≥ 3. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line. Below the reference line is overprediction and above the reference line is underprediction. Source: Livingstone *et al.*[51] (*continued*)

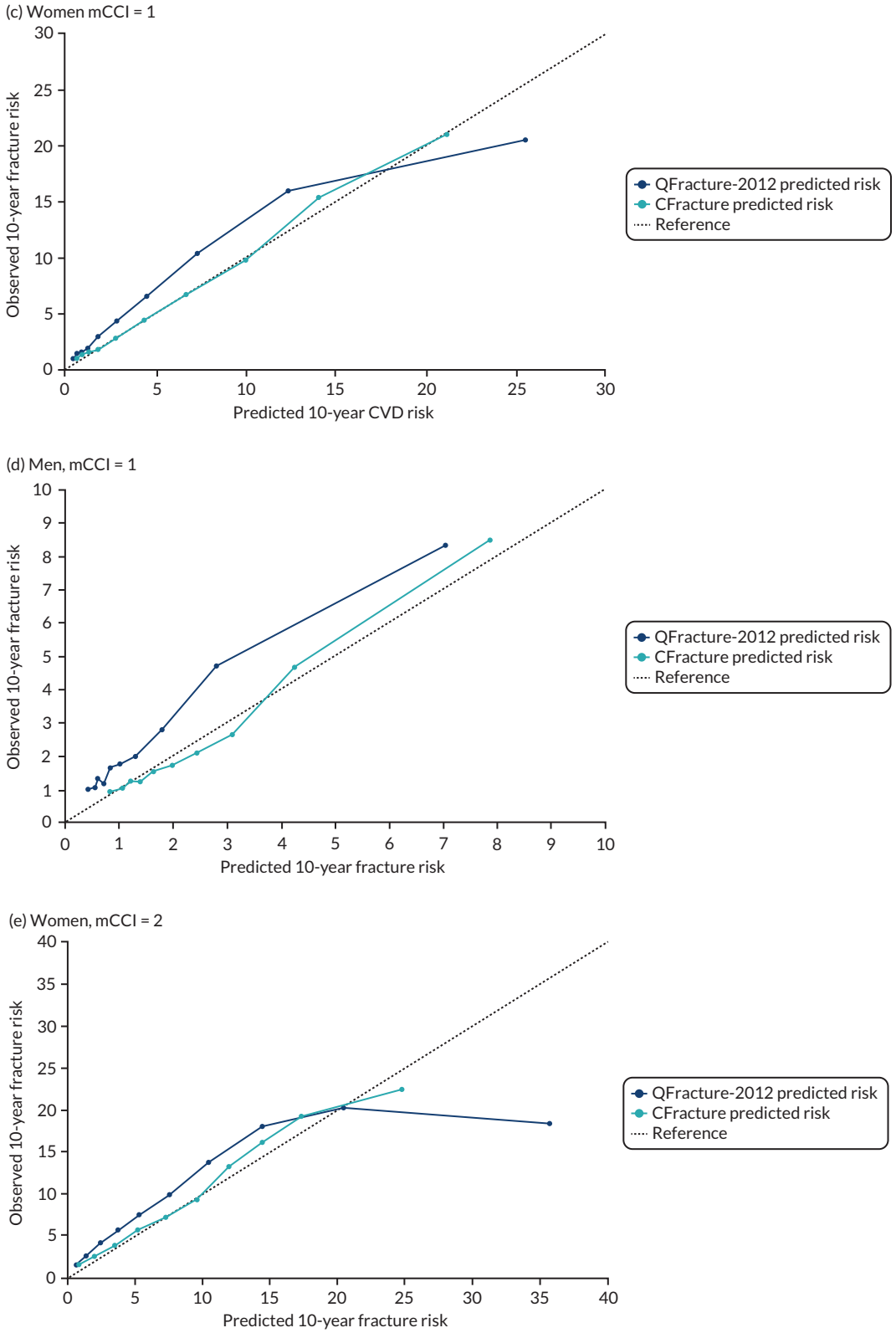


FIGURE 13 Calibration of CFracture and QFracture-2012 for MOF in the internal validation data set stratified by mCCI. (a) Women, mCCI = 0; (b) men, mCCI = 0; (c) women mCCI = 1; (d) men, mCCI = 1; (e) women, mCCI = 2; (f) men, mCCI = 2; (g) women, mCCI ≥ 3; and (h) men, mCCI ≥ 3. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line. Below the reference line is overprediction and above the reference line is underprediction. Source: Livingstone *et al.*[51] (*continued*)

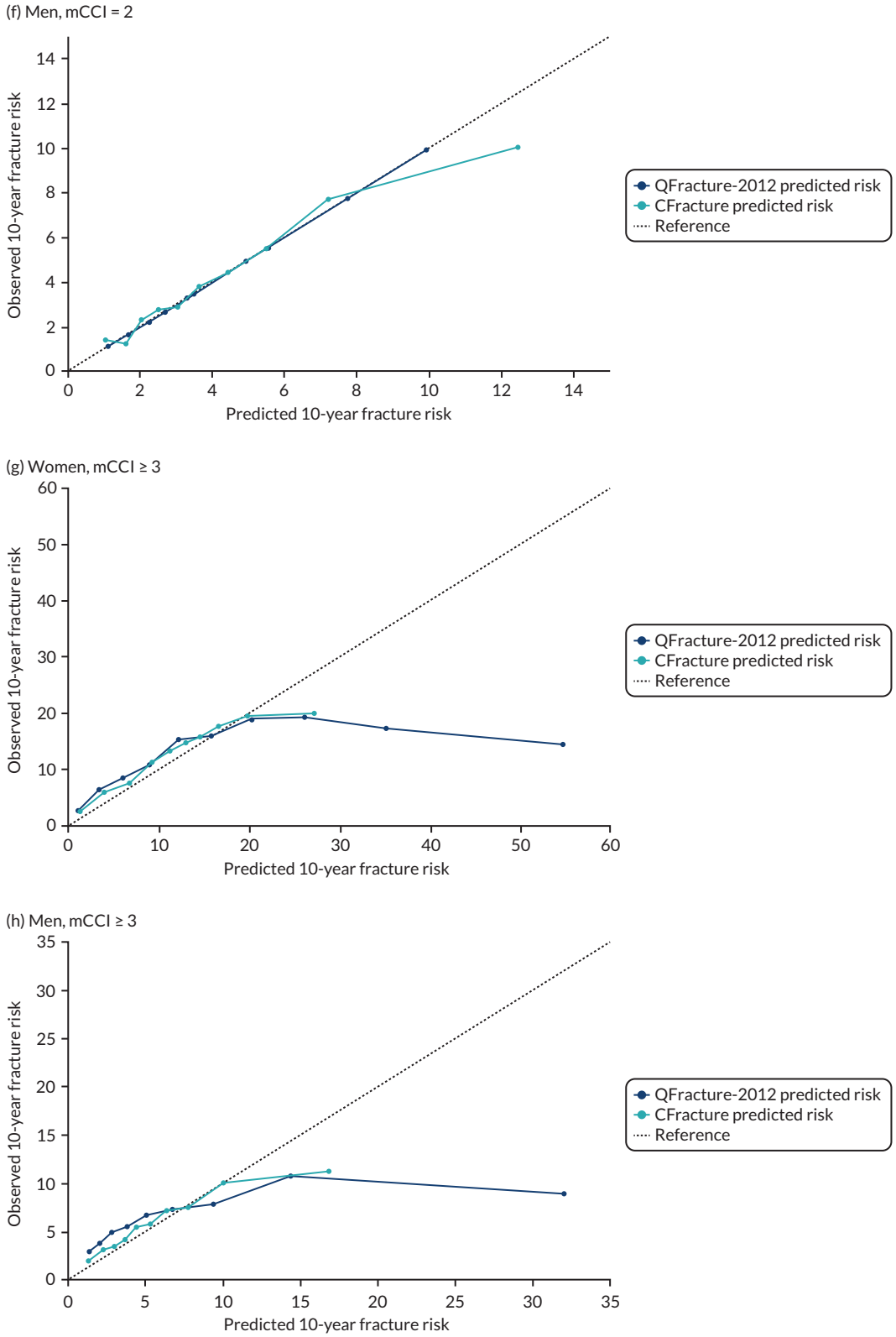


FIGURE 13 Calibration of CFracture and QFracture-2012 for MOF in the internal validation data set stratified by mCCI. (a) Women, mCCI = 0; (b) men, mCCI = 0; (c) women mCCI = 1; (d) men, mCCI = 1; (e) women, mCCI = 2; (f) men, mCCI = 2; (g) women, mCCI ≥ 3; and (h) men, mCCI ≥ 3. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line. Below the reference line is overprediction and above the reference line is underprediction. Source: Livingstone *et al.*[51]

TABLE 9 Discrimination of CFracture and QFracture-2012 for hip fracture in women and men in the validation cohort

	Women		Men	
Patient group	**CFracture, Harrell's *c*-statistic (95% CI)**	**QFracture-2012, Harrell's *c*-statistic (95% CI)**	**CFracture, Harrell's *c*-statistic (95% CI)**	**QFracture-2012, Harrell's *c*-statistic (95% CI)**
All patients	0.914 (0.908 to 0.919)	0.917 (0.912 to 0.923)	0.886 (0.877 to 0.895)	0.888 (0.879 to 0.897)
Age group (years)				
30–64	0.821 (0.805 to 0.837)	0.835 (0.819 to 0.851)	0.769 (0.751 to 0.787)	0.773 (0.754 to 0.791)
65–74	0.683 (0.671 to 0.695)	0.695 (0.683 to 0.707)	0.695 (0.676 to 0.714)	0.696 (0.677 to 0.715)
75–84	0.644 (0.636 to 0.653)	0.658 (0.649 to 0.666)	0.681 (0.666 to 0.695)	0.688 (0.673 to 0.702)
85–99	0.579 (0.567 to 0.590)	0.601 (0.589 to 0.612)	0.616 (0.591 to 0.640)	0.633 (0.608 to 0.657)
CCI				
0	0.922 (0.913 to 0.930)	0.924 (0.915 to 0.932)	0.847 (0.832 to 0.862)	0.850 (0.835 to 0.865)
1	0.893 (0.882 to 0.903)	0.897 (0.886 to 0.907)	0.866 (0.848 to 0.884)	0.872 (0.854 to 0.890)
2	0.833 (0.820 to 0.847)	0.841 (0.828 to 0.854)	0.794 (0.773 to 0.814)	0.806 (0.785 to 0.827)
≥ 3	0.767 (0.753 to 0.782)	0.783 (0.769 to 0.797)	0.770 (0.749 to 0.790)	0.780 (0.760 to 0.801)

Source: Livingstone *et al.*[51]

Calibration of CFracture for hip fracture was better than for QFracture-2012 in the whole population. Calibration was good in women across all levels of predicted risk. Calibration was good in men, except in the highest decile of predicted risk where there was underprediction (*Figure 14*). Stratified by age, calibration was good in women aged 30–64 years and 75–84 years, with some overprediction in women aged 65–74 years (*Figure 15*). In men, calibration was reasonable in those aged 30–64 years, 65–74 years and 75–84 years, with some underprediction at the highest level of predicted risk. In both men and women aged 85–99 years, calibration was poor, with overprediction at most levels of predicted risk, although was considerably better than QFracture-2012 in this age group, as well as all others.

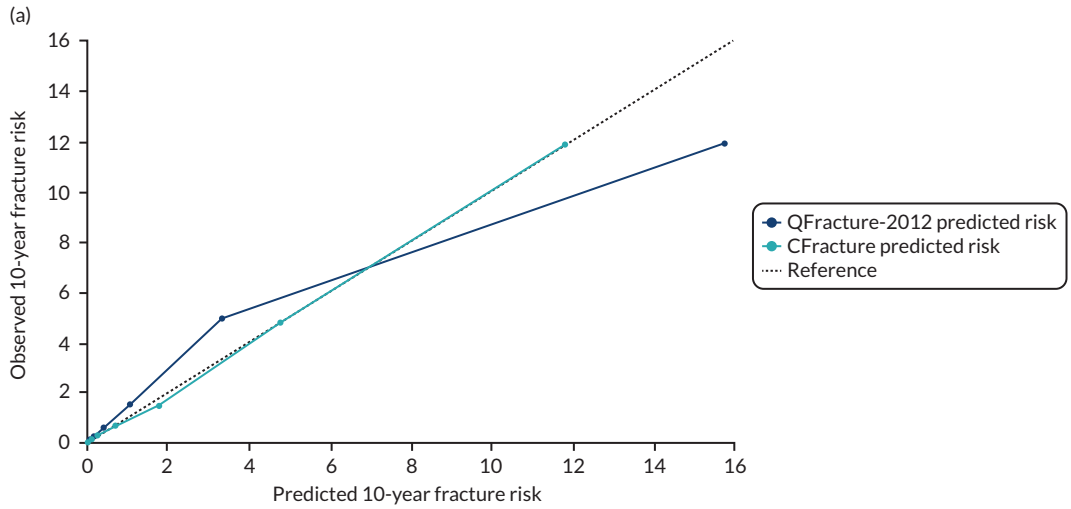


FIGURE 14 Whole-population calibration of CFracture and QFracture-2012 for hip fracture in the internal validation data set in the whole population. (a) Women; and (b) men. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Source: Livingstone *et al.*[51]

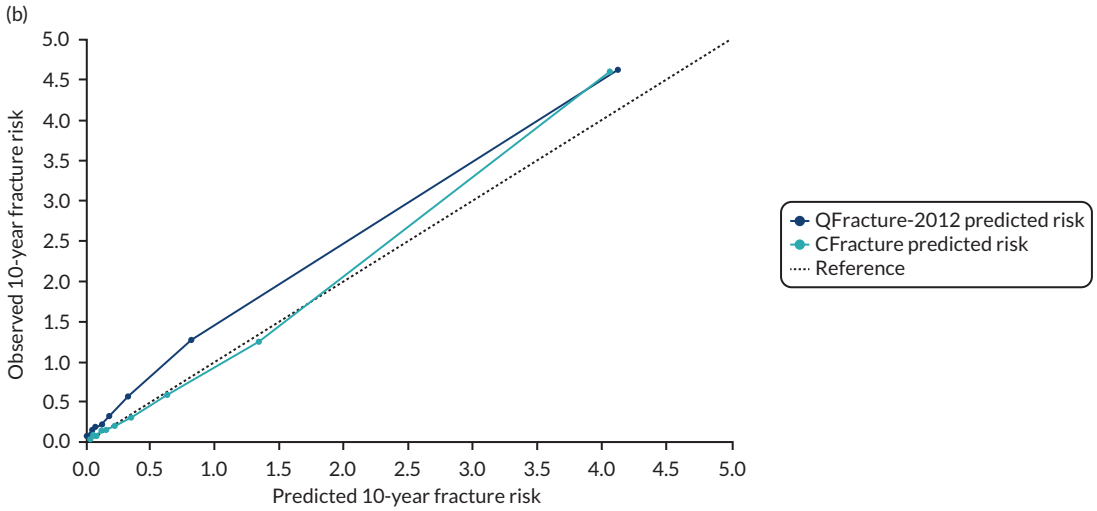


FIGURE 14 Whole-population calibration of CFracture and QFracture-2012 for hip fracture in the internal validation data set in the whole population. (a) Women; and (b) men. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Source: Livingstone *et al.*[51]

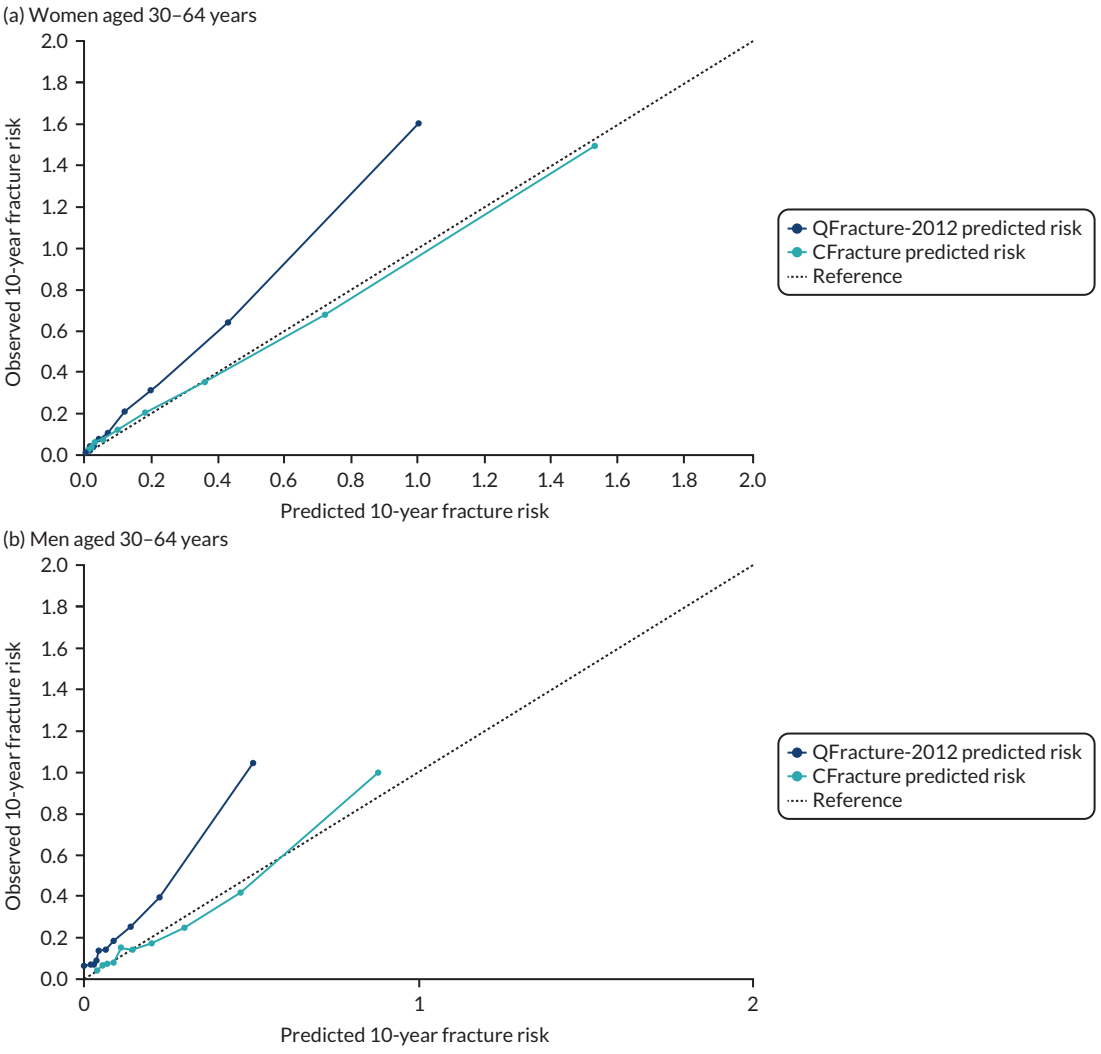


FIGURE 15 Calibration of CFracture and QFracture-2012 for hip fracture in the internal validation data set stratified by age group. (a) Women aged 30–64 years; (b) men aged 30–64 years; (c) women aged 65–74 years; (d) men aged 65–74 years; (e) women aged 75–84 years; (f) men aged 75–84 years; (g) women aged 85–99 years; and (h) men aged 85–99 years. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line. Below the reference line is overprediction and above the reference line is underprediction. Source: Livingstone *et al.*[51] (*continued*)

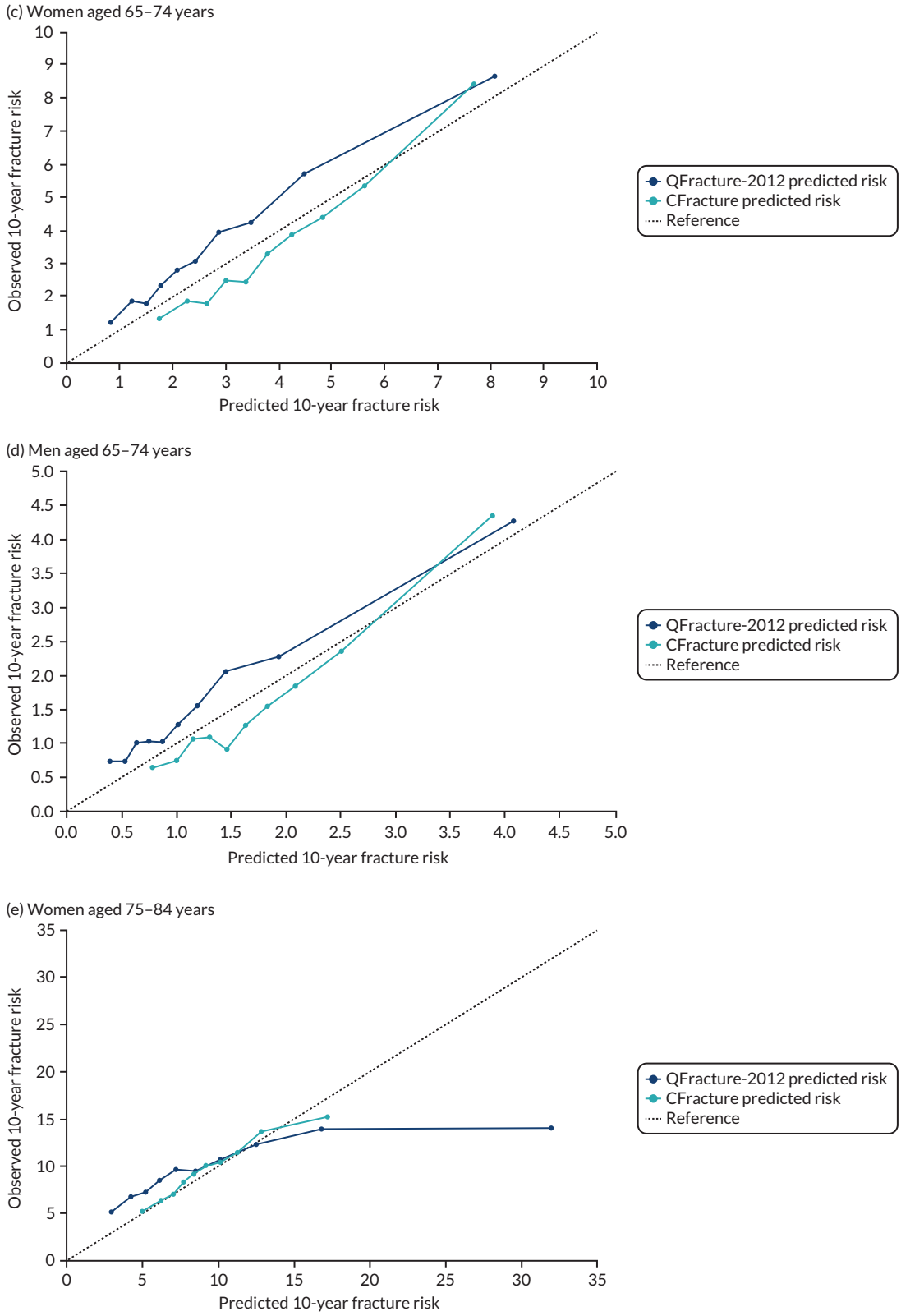


FIGURE 15 Calibration of CFracture and QFracture-2012 for hip fracture in the internal validation data set stratified by age group. (a) Women aged 30–64 years; (b) men aged 30–64 years; (c) women aged 65–74 years; (d) men aged 65–74 years; (e) women aged 75–84 years; (f) men aged 75–84 years; (g) women aged 85–99 years; and (h) men aged 85–99 years. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line. Below the reference line is overprediction and above the reference line is underprediction. Source: Livingstone *et al.*[51] (*continued*)

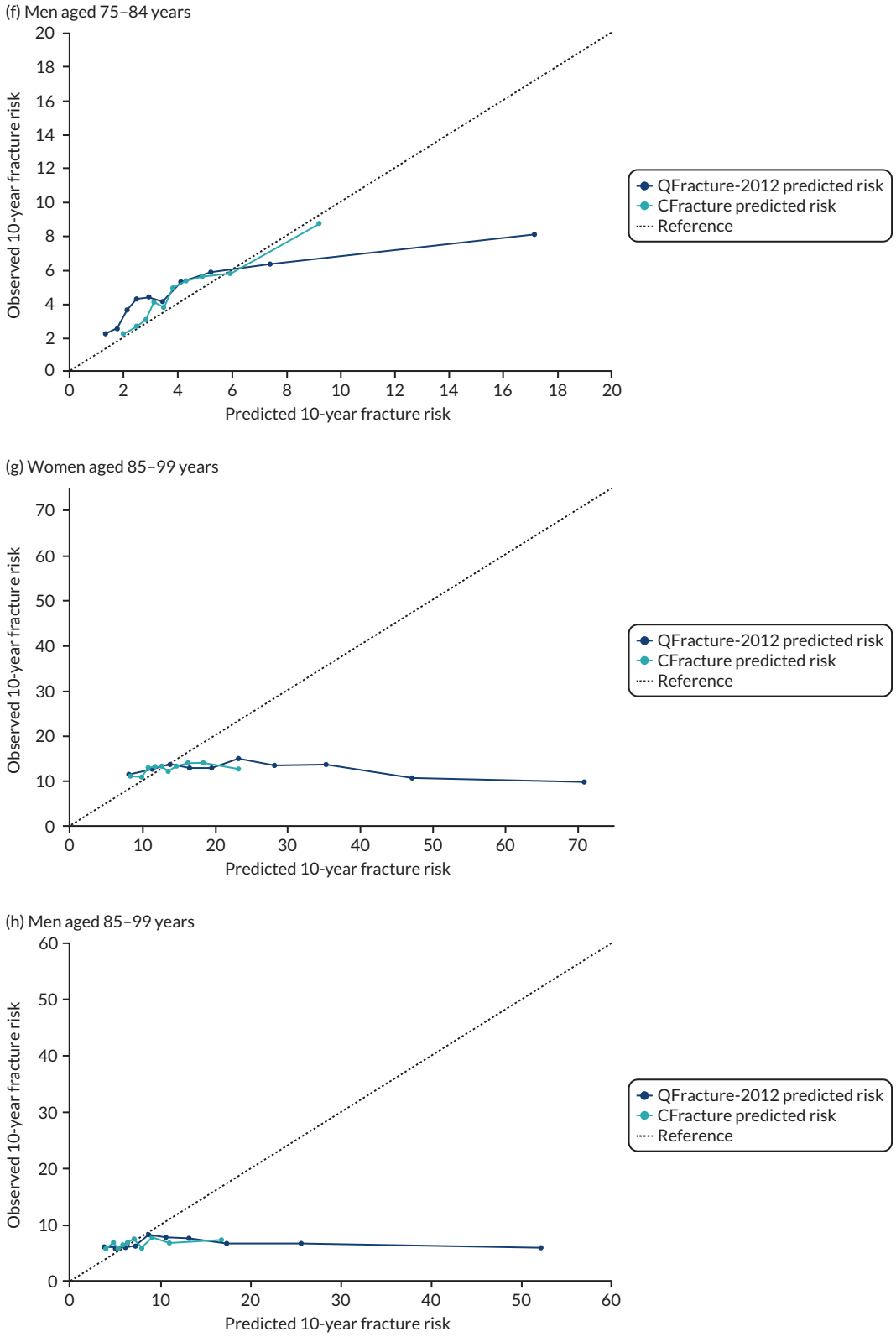


FIGURE 15 Calibration of CFracture and QFracture-2012 for hip fracture in the internal validation data set stratified by age group. (a) Women aged 30–64 years; (b) men aged 30–64 years; (c) women aged 65–74 years; (d) men aged 65–74 years; (e) women aged 75–84 years; (f) men aged 75–84 years; (g) women aged 85–99 years; and (h) men aged 85–99 years. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line. Below the reference line is overprediction and above the reference line is underprediction. Source: Livingstone *et al.*[51]

Stratified by CCI, calibration in women was good, except in the highest decile of predicted risk where there was some overprediction in CCI scores 1, 2 and ≥ 3 (*Figure 16*). Calibration in men stratified by CCI was good, apart from underprediction in the highest decile of predicted risk for CCI scores 0 and 1, underprediction in the middle of the predicted risk range for CCI score 2 and some overprediction in the highest decile of predicted risk for CCI score ≥ 3.

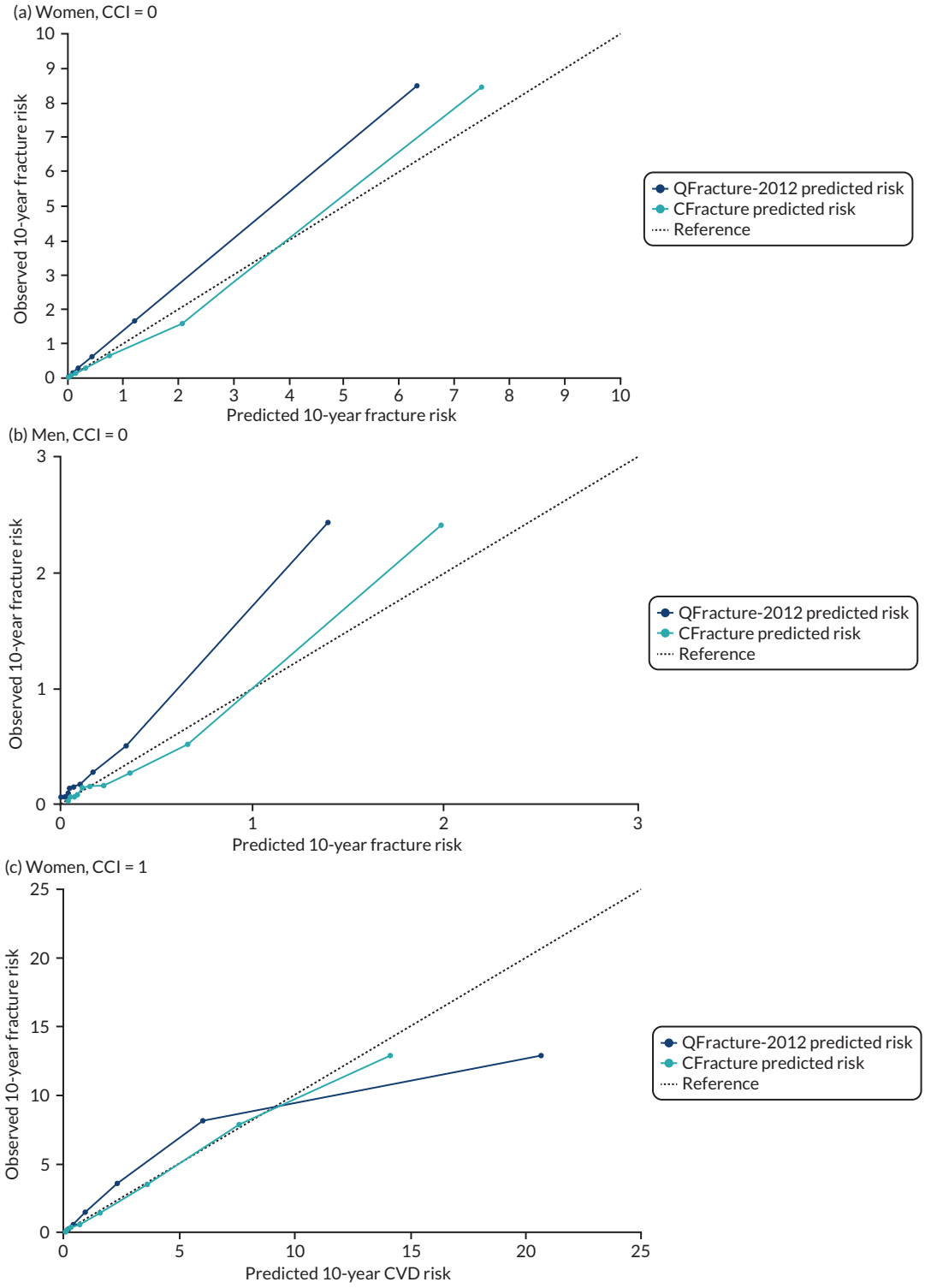


FIGURE 16 Calibration of CFracture and QFracture-2012 for hip fracture in the internal validation data set stratified by CCI. (a) Women, CCI = 0; (b) men, CCI = 0; (c) women, CCI = 1; (d) men, CCI = 1; (e) women, CCI = 2; (f) men, CCI = 2; (g) women, CCI ≥ 3; and (h) men, CCI ≥ 3. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line. Below the reference line is overprediction and above the reference line is underprediction. Source: Livingstone *et al.*[51] (*continued*)

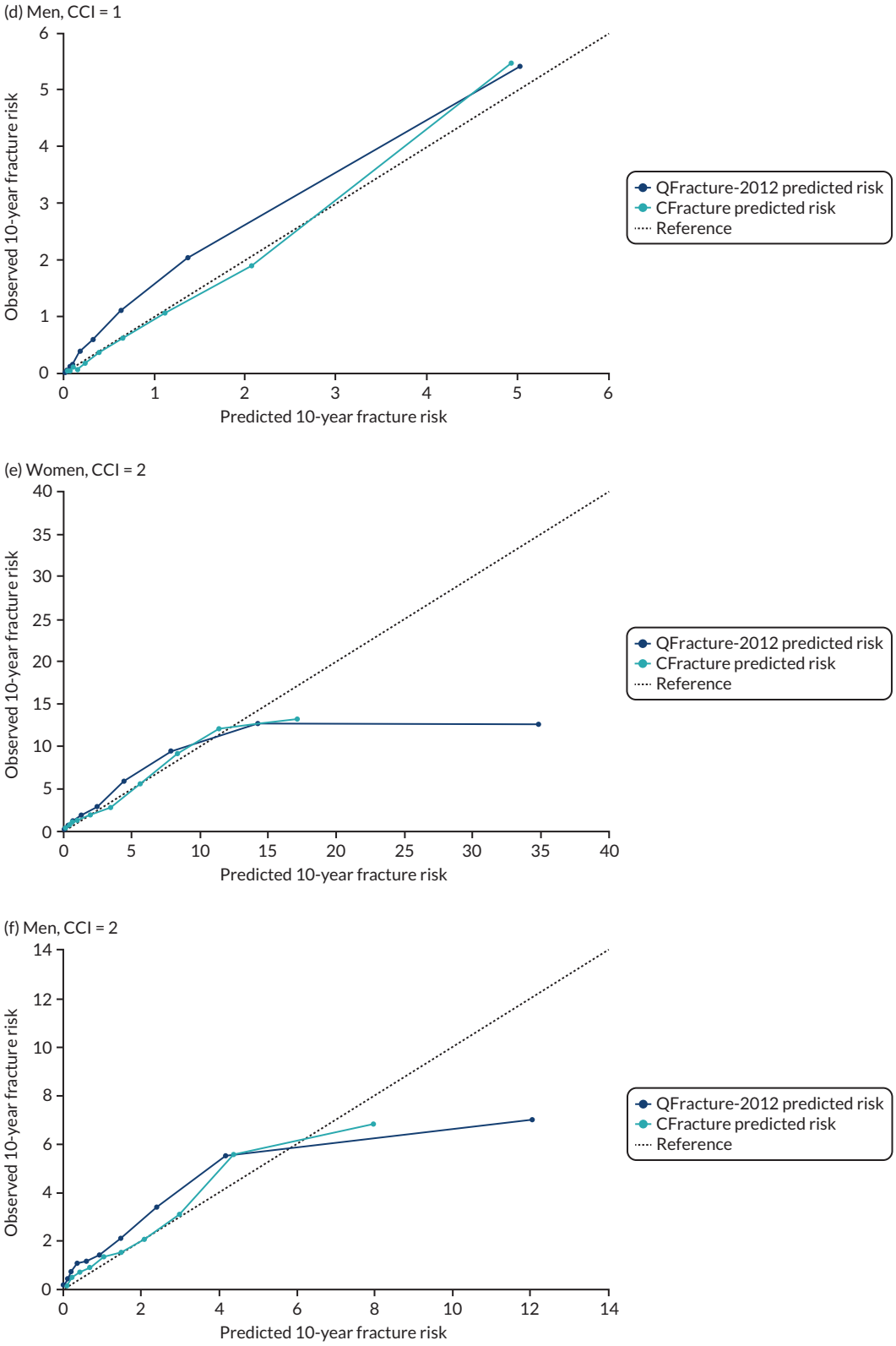


FIGURE 16 Calibration of CFracture and QFracture-2012 for hip fracture in the internal validation data set stratified by CCI. (a) Women, CCI = 0; (b) men, CCI = 0; (c) women, CCI = 1; (d) men, CCI = 1; (e) women, CCI = 2; (f) men, CCI = 2; (g) women, CCI ≥ 3; and (h) men, CCI ≥ 3. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line. Below the reference line is overprediction and above the reference line is underprediction. Source: Livingstone *et al.*[51] (*continued*)

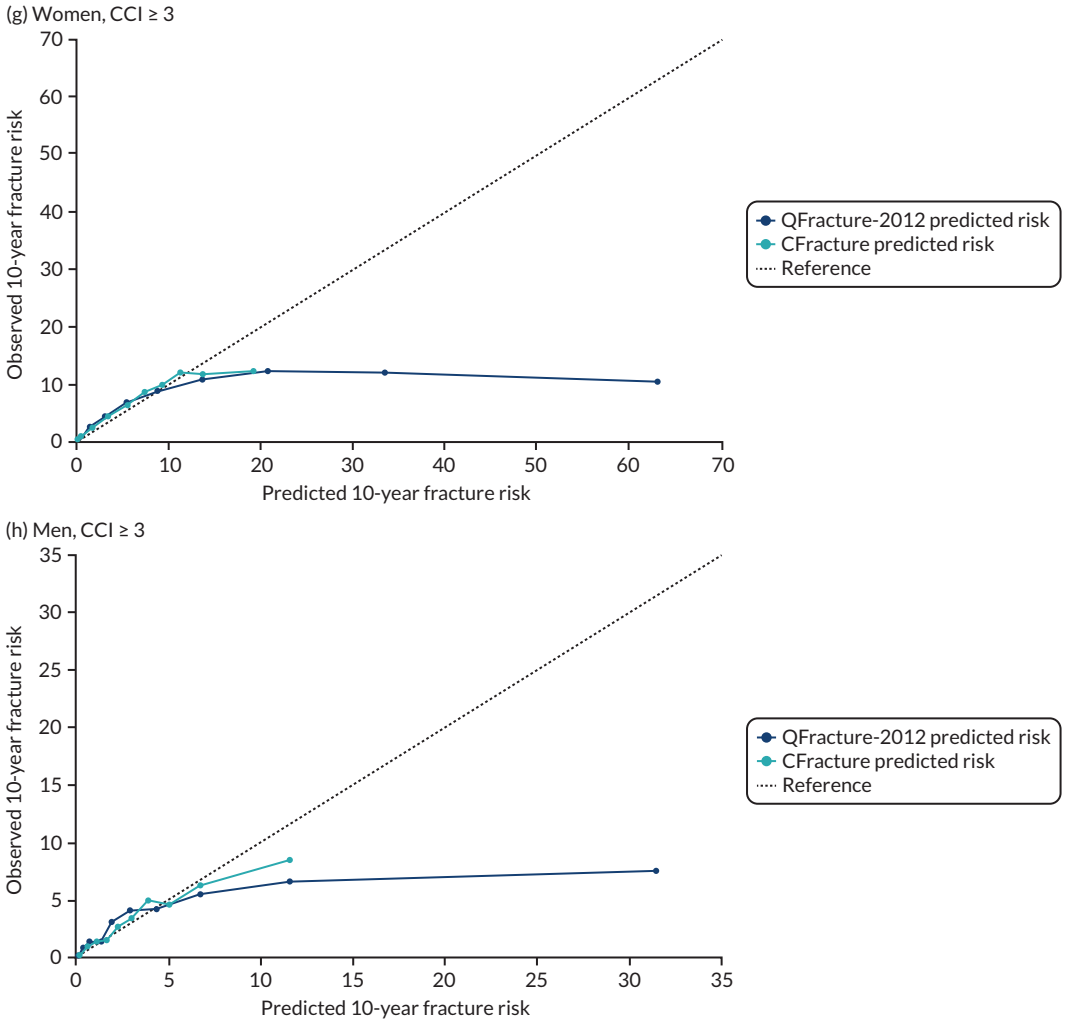


FIGURE 16 Calibration of CFracture and QFracture-2012 for hip fracture in the internal validation data set stratified by CCI. (a) Women, CCI = 0; (b) men, CCI = 0; (c) women, CCI = 1; (d) men, CCI = 1; (e) women, CCI = 2; (f) men, CCI = 2; (g) women, CCI ≥ 3; and (h) men, CCI ≥ 3. Observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. Ideal calibration lies on the reference line. Below the reference line is overprediction and above the reference line is underprediction. Source: Livingstone *et al.*[51]

Summary

QFracture-2012 external validation

QFracture-2012 was found to have very good to excellent discrimination in the total population, with higher discrimination observed in the hip fracture model than in the MOF model. However, discrimination was typically only poor to moderate in important subgroups, including older patients (as expected given that age is such a strong predictor of risk[72,100]) and moderate to good those with higher levels of multimorbidity. However, calibration was very poor, irrespective of how evaluated. When evaluated in its own terms (ignoring competing risk), QFracture-2012 showed consistent underprediction for both MOF and hip fracture. The most likely explanation for this underprediction is that fracture ascertainment in this study is more complete, as it includes fractures recorded during hospital admission in addition to fractures recorded in GP electronic health records and mortality registration data. For hip fracture, the inclusion of hospital data for fracture ascertainment likely explained much of the observed difference in hip fracture incidence, but less than half of observed differences in MOF incidence. Other reasons for higher observed incidence are the use of different index dates for first study entry (1 January 2004 in this study vs. 1 January 1998 in QFracture-2012), as recording of fractures in GP data is likely to have improved over time, as well as the use of different codesets to identify fracture (although QFracture-2012 does not have a published list of Read codes for predictors and so direct comparison is not possible).

When evaluated against observed fractures estimated accounting for competing risk, in general, underprediction reduced (i.e. failing to account for competing risk causes overprediction); however, there was very large overprediction at higher levels of predicted risk in older people and in people with more complex multimorbidity. Notably, in people aged 85–99 years and with CCI score ≥ 3, calibration was extremely poor, with observed risk flat or even declining across deciles of increasing predicted risk. Therefore, in summary, QFracture-2012 has two causes of poor calibration that operate in different directions. First, QFracture-2012 considerably underpredicts in all patients because derivation is based on incomplete ascertainment of fracture. Second, QFracture-2012 considerably overpredicts in people with high competing risk of death (primarily older people and in people with more complex multimorbidity).

CFracture derivation and internal validation

In the internal validation cohort, discrimination of CFracture for MOF and hip fracture in the whole population was good to excellent for MOF and excellent for hip fracture, and was similar to QFracture-2012 performance in the same data set. Stratified by age, CFracture discrimination was less good in all age groups, with worse discrimination with increasing age, except in men with MOF, for whom there was no obvious relationship with age. Stratified by CCI, discrimination for MOF was somewhat worse in all strata than in the whole population, but there was no clear pattern with age. Stratified by CCI, discrimination for hip fracture was similar to the whole population for a CCI score of 0, but discrimination declined somewhat with increasing comorbidity (although was good to excellent in all strata).

CFracture was better calibrated than QFracture-2012 in the whole population and in every strata, although was better calibrated in women than men and was better calibrated for hip fracture than for MOF. Strikingly, however, CFracture was poorly calibrated in women and men aged 85–99 years (although much less so than QFracture-2012).

These findings are somewhat different from previous external validations.[18,19] The first version of QFracture-2012[17] was independently, externally validated in The Health Improvement Network data set, which is a similar (and partially overlapping) set of practices to CPRD. This study found QFracture-2012 to have excellent discrimination and calibration in the whole population.[18] The updated QFracture-2012 (as evaluated in this study)[26] was externally validated in CPRD by the QFracture-2012 derivation team, and this study, again, found excellent discrimination and calibration in the whole population.[19] This study differs from both previous external validations in two ways. First, we also identified fractures recorded during hospital admission, whereas the two previous studies identified fractures recorded in GP records and mortality registration data only. Better ascertainment of fractures would be expected to lead to underprediction of risk, as observed in this study. An Israeli external validation using both community and hospital data for ascertainment also observed considerable underprediction by QFracture-2012, consistent with our findings.[92] Second, this study examined calibration against observed outcomes estimated in the same way as previous external validations (using the Kaplan–Meier estimator, which ignores competing risk) and additionally accounting for competing risk (using the Aalen–Johansen estimator). As not accounting for competing risk leads to overprediction of fractures, this partially, but not completely, compensated for the observed underprediction in the whole population. However, as expected,[96,97,100] accounting for competing risks led to large changes in observed risk in older people and in people with more multimorbidity, consistent with systematic overprediction by QFracture-2012 in groups with high competing mortality (despite systematic underprediction due to incomplete fracture ascertainment in QFracture-2012 derivation).

Limitations

This study has the same limitations as any routine data study (see *Chapter 2*, *Limitations*), but several particular limitations specifically apply. First, the observed incidence of fracture is higher in this study than in QFracture-2012 derivation and the two previous external validations.[18,19,26] There are three possible reasons for this. First, this study used hospital data to identify fractures (which accounts for most of the difference for hip fracture and some of the difference for MOF). Second, this study has

an earliest study entry date of 1 January 2004 compared with the original QFracture-2012 external validation date of 27 June 1994 and the updated version external validation date of 1 January 1998, and recording of fracture outcomes in GP data are likely to have improved over time. Third, the codes used to identify fractures in GP data may be different; however, because none of the previous studies published their codesets we cannot explore this further. Within our own data, one issue is that humeral fractures were most commonly recorded in the GP data without specifying whether proximal or more distal. Therefore, we included non-site-specific humeral fractures as 'proximal humerus' fractures, which may lead to some misclassification (i.e. some false positives). However, registry data show that ≈ 80% of humeral fractures are proximal (and > 80% of non-proximal fractures are also low energy)[101] and only including humeral fractures specified as proximal would lead to larger misclassification (i.e. a larger number of false negatives).

Second, although we explicitly accounted for censoring due to death in this study, the analysis still assumes that people who deregister from a CPRD practice have the same fracture risk as people who do not. This assumption is likely to be strong in older people for whom deregistration due to moving into extra-care housing or a care home is likely to be associated with higher falls and fracture risk.

Chapter 5 Quantifying direct treatment disutility associated with preventative treatments

Background

There is a growing evidence base that taking a specific treatment, particularly one requiring long-term use for a chronic condition, can cause inconvenience or 'disutility' to a patient that is distinct from the unwanted harms, adverse outcomes or specific effects of the treatment. DTD is a type of process disutility[102] related to the inconvenience of obtaining prescriptions and medicines, needing to modify lifestyles to take medicines and attending healthcare visits for monitoring treatment.[40] DTD may have particular relevance for long-term medication use, such as statins for the primary prevention of CVD and bisphosphonates for osteoporosis, as the benefits of treatment are typically small and accrue over long periods, while any inconvenience, however small, is likely to start with treatment initiation and may be persistent.

Existing empirical studies have estimated a range of values of DTD, with the general size of the disutility being around 0.01 on average, which is equivalent to a loss of ≈ 3.6 days of perfect health over 1 year.[47,48,103] With these sorts of DTD values, several primary preventative treatments for CVD have switched from meeting acceptable levels of cost-effectiveness to not being cost-effective.[2,44,46,104–109] The mechanism underpinning this change is a simple one, whereby the DTD value is much larger than the expected health benefits of the medicine over the longer term. However, DTD input values have been elicited empirically in only a few studies, several of which have either adopted small study sizes[47] or sampling frames which are not representative of either patients[48] or the general population.[103] Consequently, there is considerable uncertainty as to the actual size and distribution of DTD values, whether or not DTD changes with the experience of taking medicines and, consequently, whether or not these values could, and should, be used to inform decision-making.

Aim and objectives

The study reported in this chapter addresses objective 4:

- To quantify the magnitude, variation and distribution of DTD (i.e. the disutility incurred by taking a regular, long-term treatment irrespective of drug-specific side effects) in the general and statin- or bisphosphonate-treated populations.

This study had two specific objectives:

1. To elicit values for DTD for two exemplars of medicines using time trade-off (TTO).
2. To elicit values for DTD for two exemplars of medicines using best–worst scaling (BWS).

Methods

This study used two types of preference elicitation methods: (1) TTO and (2) BWS.

Selection of exemplar medicines

We quantified the DTD of statins for the primary prevention of heart disease and bisphosphonates for the primary prevention of fractures using two medicine-taking case studies. Statins were chosen as an example of a class of medicines that are perceived by professionals to be benign, but which some people perceive as harmful. Bisphosphonates were selected because they are medicines we thought had an obvious influence on daily life (i.e. people who take a bisphosphonate are required to drink a large glass of water before taking the medication, remain upright for 30 minutes after taking it and avoid food and drink for 2 hours thereafter).

Selection of elicitation methods

We sought to get an accurate description of the medicine-taking health states within our survey so that our respondents could appropriately value them. In addition, we wanted to check that the methods we adopted were appropriate and robust enough to estimate small disutilities associated with the ongoing use of a medicine. Therefore, we reviewed methods from previous studies[47,48,103] that had attempted to estimate DTD values and integrated those methods with the experience and views of our clinical research team, as well as our two patient representatives who were members of the research team. This review suggested that TTO should be the predominant method, but that there is emerging interest in using BWS to elicit DTD.

The context

The elicitation surveys were designed to take account of the specific context in which a respondent is taking a medicine for primary prevention. Two distinct surveys for each method (i.e. TTO and BWS) were designed to focus on each of the two exemplars of statins and bisphosphonates.

For each exemplar, respondents were asked to consider taking medicine A, which was a 'one-off pill' assumed to have no ongoing inconvenience, or medicine B, which was a daily pill for 10 years. In the TTO exercise, we also decided to include four scenarios to understand whether or not DTD values differed based on how the benefits and harms of the medication were framed. Therefore, we asked our respondents to consider medicines A and B in the context of the pills having (1) no side effects, (2) minor side effects (MSEs), (3) severe side effects (SSEs) and (4) reduced effectiveness. Finally, we also wanted to explore if there was any systematic difference between how different groups might value DTDs. In particular, we wanted to understand whether or not patients with experience of taking pills valued DTD differently from people with little or no experience. In addition, we thought it was important to explore other factors, such as age and sex.

Time trade-off exercise

The first method we selected to value the disutility of medicine-taking health states was the TTO method. TTOs are a widely used approach for eliciting utility values and were used to generate the valuations for the EuroQol-5 Dimensions, three-level version (EQ-5D-3L) health states, which are part of the current NICE reference case. In general, the TTO method involves asking respondents to consider the relative amounts of time (e.g. number of life-years) they would be willing to sacrifice to avoid a poorer health state.[110] In this study, the TTO method followed the approach taken by Hutchins *et al.*[48,103] and asked respondents the maximum amount of time they are willing to give up at the end of their life to avoid having to take a medicine. Per respondent, for each of the four questions, the estimated utility was calculated as the ratio x/t, where x is the final selected time period for the medicine A option (i.e. one pill taken once) and t is the full life-years assumed for the medicine B option (i.e. a pill taken every day for 10 years).[111]

Best–worst scaling experiment

Best–worst scaling experiments are an extension of discrete choice experiments.[112] There are three types of BWS: case 1 (object case), case two (profile case) and case three (multiprofile case).[113] This study used a case 2 (profile case) BWS experiment. A profile case BWS experiments ask respondents to select their most preferred and least preferred items (defined by attributes and levels) in a question.

An argued advantage of profile case BWS over standard discrete choice experiments is that the choices made reveal more information about the relative strength of people's preferences for each attribute in the design, using fewer questions, which could, in turn, reduce the response error. Importantly, using a BWS allows a rank ordering of the attributes in the experiment together with utility weights to be estimated. In this study, the BWS experiment was framed around the choice question 'we want you to indicate which of the listed features of medicine A you think are the most and least likely to make you want to avoid taking the tablet'. The BWS experiment contained three attributes: (1) inconvenience (levels: no inconvenience and inconvenience), (2) probability of a MSE (levels: 1%, 5%, 9% and 13%) and (3) probability of a SSE (levels: 0.1%, 0.3%, 0.5% and 0.7%). Rapid reviews of the relevant published literature and input from the research team, including patient involvement, were used to generate a list of potential attributes and assigned levels. The BWS exercise was created using a full factorial design of 32 choice sets, which were split into four randomised blocks. Each respondent was assigned to one of the four blocks, comprising eight choice sets, with each choice set displaying three features of medicine A (i.e. inconvenience, MSE and SSE). The levels for these three features varied across choice sets.

Design of training materials

Consistent with emerging good practice in the design of a stated-preference study, training materials, that introduced the background for each case study (i.e. statin or bisphosphonate) and the attributes and levels used in the BWS exercise were created using a storyboard approach.[114] The same training materials were used for the TTO and BWS experiment. In addition, we used visual arrays to communicate absolute risk consistent with best practice.[115]

Survey format and content

Online surveys were designed for each method (i.e. TTO and BWS), using the same approach and format for each exemplar medicine (i.e. statins and bisphosphonates). The surveys were formatted and administered online using Sawtooth software (Sawtooth Software, Inc., Provo, UT, USA). Respondents were sent a secure link to complete one of the surveys (no reminders were used). There were three parts to each survey. The first part of the survey consisted of the EQ-5D-3L questions, training materials and questions about the respondent's attitude towards taking a medicine for the first time. The second part of the survey consisted of the main elicitation exercise (i.e. TTO or BWS). The third part of the survey included questions about whether respondents were currently taking or had ever taken one of the branded bisphosphonates (or statins), respondents' perceived benefits and harms of bisphosphonates (or statins), whether or not respondents had experienced any side effects from bisphosphonates (or statins) and whether or not respondents found it inconvenient to take the medicine. Participants were also asked about their opinion on taking the medicine (i.e. whether they mind/dislike taking it), whether or not they took any other medicines, the number of medicines taken on a regular basis, the number of times medicines are taken daily and sociodemographic questions, such as age, gender, qualifications, employment status, ethnicity and religion. There were also non-compulsory probability questions to understand the respondents' understanding of risk. Feedback questions towards the end of the survey included asking respondents about their confidence in making similar choices in real life, their perceived difficulty in making choices between alternatives and in understanding the survey, as well as general feedback comments to improve the clarity of the survey.

Piloting of experiments

Two pilot phases were conducted for the design of each experiment. For the TTO and BWS surveys, early piloting involved 'think-aloud' interviews with a sample of 19 patients recruited from a general practice in Greater Manchester. The intention of the early pilot was to understand whether or not the draft surveys, training materials and valuation exercises were sufficiently clear for respondents. We also wanted to understand how our respondents were interacting with the material presented. Following on from this, a few minor changes were made to the training materials and valuation exercise. The survey was then tested again in quantitative pilot studies involving members of the public to assess whether or not the data could be analysed from the survey design. No changes were made following

the quantitative pilot study. The final elicitation studies were then launched and involved a sample of members of the public and a sample of people with experience of taking a statin or bisphosphonate.

Data samples

People with experience of taking a statin or bisphosphonate were recruited from general practices via the NHS Research Scotland Primary Care Network and the Scottish Health Research Register (SHARE which is a register of people living in Scotland, allowing recruitment after a search of their medical records). To be included, patients needed to have been prescribed a statin or bisphosphonate in the previous year, needed to be aged ≥ 30 years and should not have been diagnosed for dementia or be taking a drug for dementia. Members of the public for the valuation study were recruited online using the panel company Dynata (Shelton, CT, USA). Within this sample, we also identified members of the public with experience of taking a statin or bisphosphonate. Respondents to the online survey needed to be aged over ≥ 30 years, but otherwise the sample should be a demographically balanced representation of the general public willing to take an online survey.

Results

The results are presented in two distinct sections for the TTO and BWS experiments.

Time trade-off

Analysis characteristics for respondents to the TTO for statins (n = 514) and respondents to the TTO for bisphosphonates (n = 365) are reported in *Table 10*. Statin patients tended to report marginally higher mean TTO values than public respondents [difference 0.007 (SE 0.003); i.e. the amount of life expectancy respondents were willing to sacrifice to avoid taking statins was 0.7 percentage points greater in the public respondents than in people with experience of statins], although this finding was not statistically significant. Bisphosphonate patients reported much higher TTO values – indicating less DTD – than public respondents [difference 0.024 (SE 0.006)], with this difference being statistically significant. For both statins and bisphosphonates, changing the question context did not alter the

TABLE 10 Description of the sample characteristics completing the TTO

Characteristic	Statin survey			Bisphosphonate survey			Total (n = 879)
	Patient[a] (n = 227)	Public[b] (n = 287)	Total (n = 514)	Patient[a] (n = 86)	Public[b] (n = 279)	Total (n = 365)	
Age (years), *n* (%)							
< 35	1 (0.7)	14 (6.1)	15 (4.0)	0 (0.0)	18 (7.9)	18 (6.8)	33 (5.2)
35–44	4 (2.8)	44 (19.1)	48 (12.9)	1 (2.7)	42 (18.5)	43 (16.3)	91 (14.3)
45–54	6 (4.2)	46 (20.0)	52 (14.0)	2 (5.4)	32 (14.1)	34 (12.9)	86 (13.5)
55–64	43 (30.3)	63 (27.4)	106 (28.5)	10 (27.0)	45 (19.8)	55 (20.8)	161 (25.3)
65–74	66 (46.5)	60 (26.1)	126 (33.9)	15 (40.5)	80 (35.2)	95 (36.0)	221 (34.7)
≥ 75	22 (15.5)	3 (1.3)	25 (6.7)	9 (24.3)	10 (4.4)	19 (7.2)	44 (6.9)
Missing	85	57	142	49	52	101	243
Sex, *n* (%)							
Female	49 (34.5)	115 (50.0)	164 (44.1)	33 (89.2)	141 (62.4)	174 (66.2)	338 (53.2)
Male	93 (65.5)	115 (50.0)	208 (55.9)	4 (10.8)	85 (37.6)	89 (33.8)	297 (46.8)
Missing	85	57	142	49	53	102	244

TABLE 10 Description of the sample characteristics completing the TTO (*continued*)

Characteristic	Statin survey			Bisphosphonate survey			Total
	Patient[a] (*n* = 227)	Public[b] (*n* = 287)	Total (*n* = 514)	Patient[a] (*n* = 86)	Public[b] (*n* = 279)	Total (*n* = 365)	(*n* = 879)
Ethnicity, *n* (%)							
White British/Irish	133 (93.7)	211 (91.7)	344 (92.5)	36 (97.3)	203 (89.4)	239 (90.5)	583 (91.7)
White other	3 (2.1)	10 (4.3)	13 (3.5)	1 (2.7)	8 (3.5)	9 (3.4)	22 (3.5)
Mixed/multiple ethnic origins	0 (0.0)	1 (0.4)	1 (0.3)	0 (0.0)	5 (2.2)	5 (1.9)	6 (0.9)
Black/African/ Caribbean/Black British	0 (0.0)	3 (1.3)	3 (0.8)	0 (0.0)	2 (0.9)	2 (0.8)	5 (0.8)
Asian/Asian British	0 (0.0)	4 (1.7)	4 (1.1)	0 (0.0)	7 (3.1)	7 (2.7)	11 (1.7)
Chinese	0 (0.0)	1 (0.4)	1 (0.3)	0 (0.0)	2 (0.9)	2 (0.8)	3 (0.5)
Other ethnicity	6 (4.2)	0 (0.0)	6 (1.6)	0 (0)	0 (0)	0 (0)	6 (0.9)
Missing	85	57	142	49	52	101	243
Number of pills taken daily, *n* (%)							
0	0 (0.0)	91 (39.6)	91 (24.5)	0 (0.0)	77 (33.9)	77 (29.2)	168 (26.4)
1	4 (2.8)	52 (22.6)	56 (15.1)	4 (10.8)	38 (16.7)	42 (15.9)	98 (15.4)
2–5	104 (73.2)	69 (30.0)	173 (46.5)	23 (62.2)	86 (37.9)	109 (41.3)	282 (44.3)
6–10	31 (21.8)	14 (6.1)	45 (12.1)	5 (13.5)	16 (7.0)	21 (8.0)	66 (10.4)
> 10	3 (2.1)	4 (1.7)	7 (1.9)	5 (13.5)	10 (4.4)	15 (5.7)	22 (3.5)
Missing	85	57	142	49	52	101	243
Number of different times pill taken per day, *n* (%)							
None	3 (2.1)	94 (40.9)	97 (26.1)	0 (0.0)	75 (33.0)	75 (28.4)	172 (27.0)
Once per day	33 (23.2)	74 (32.2)	107 (28.8)	18 (48.6)	75 (33.0)	93 (35.2)	200 (31.4)
Two times a day	87 (61.3)	48 (20.9)	135 (36.3)	12 (32.4)	54 (23.8)	66 (25.0)	201 (31.6)
Three times a day	17 (12.0)	11 (4.8)	28 (7.5)	5 (13.5)	19 (8.4)	24 (9.1)	52 (8.2)
More than three times a day	2 (1.4)	3 (1.3)	5 (1.3)	2 (5.4)	4 (1.8)	6 (2.3)	11 (1.7)
Missing	85	57	142	49	52	101	243
EQ-5D-3L utility mean (SD)[c]	0.827 (0.2)	0.818 (0.2)	0.822 (0.2)	0.770 (0.2)	0.786 (0.2)	0.783 (0.2)	0.806 (0.2)
Missing	56	41	97	35	33	68	165

SD, standard deviation.
a Patient sample was recruited from GPs in the NHS Research Scotland Primary Care Network or SHARE.
b Public sample was recruited from Dynata.
c Health status measured using the EQ-5D-3L and transformed into a utility score using Dolan.[116]

mean TTO scores by more than 0.01. Irrespective of the type of question or respondent, there was a clear difference between statins and bisphosphonates survey results (*Figure 17*). Mean TTO values for the entire statin sample (0.967) were higher than TTO scores for the bisphosphonate sample (0.933), meaning that the average respondent was willing to trade twice as much life expectancy to avoid bisphosphonates as they would to avoid statins [0.033 vs. 0.067; absolute difference 0.034 (SE 0.004)] (*Table 11*). Respondents who had experience of taking medications more than three times a day provided

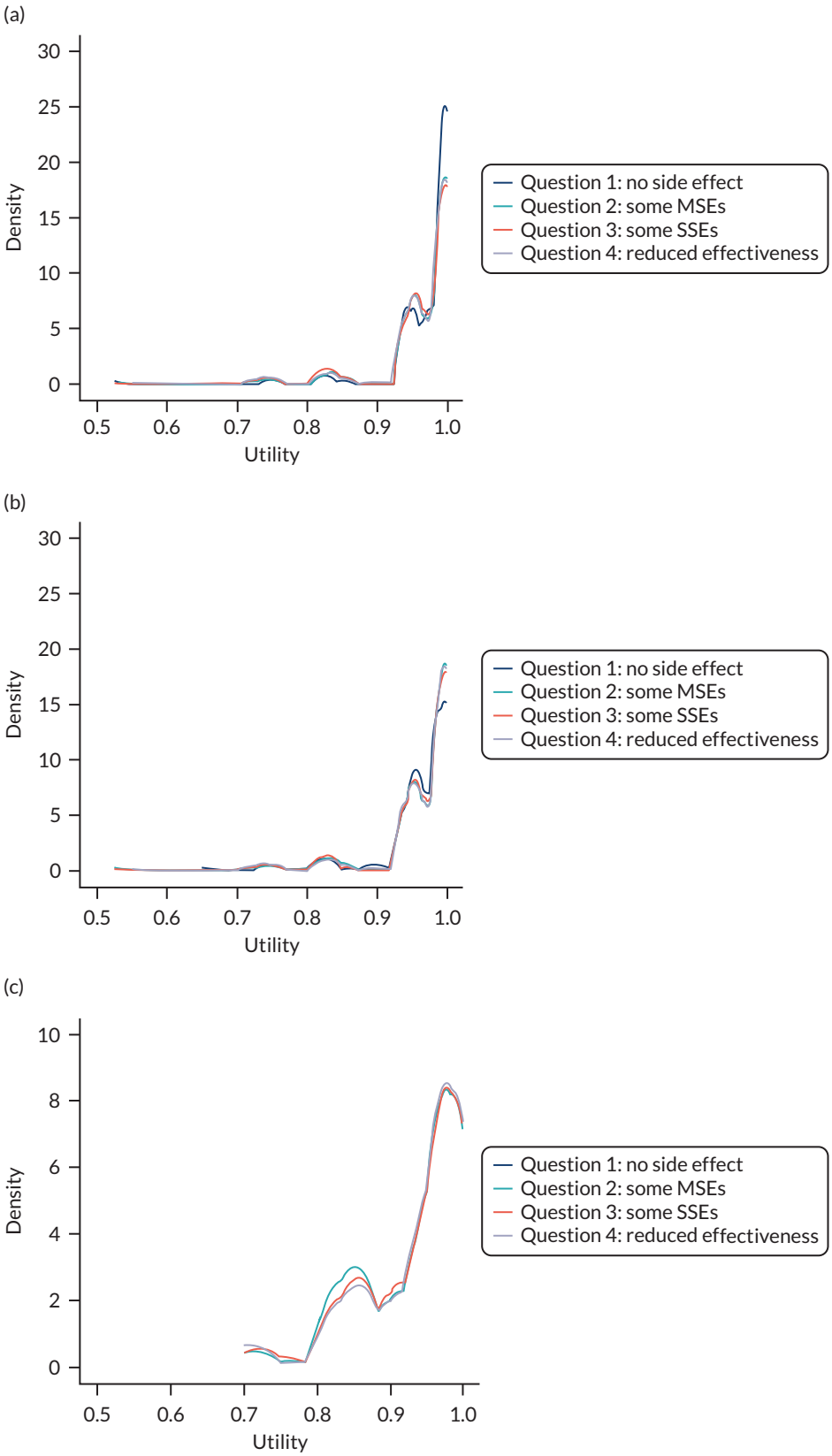


FIGURE 17 Kernel density plots showing distribution of TTO responses stratified by medicine, question context and respondent type. (a) Statin questions 1–4 utility values in patients; (b) statin questions 1–4 utility values in the public; (c) bisphosphonates questions 1–4 utility values in patients; and (d) bisphosphonates questions 1–4 utility values in the public. (*continued*)

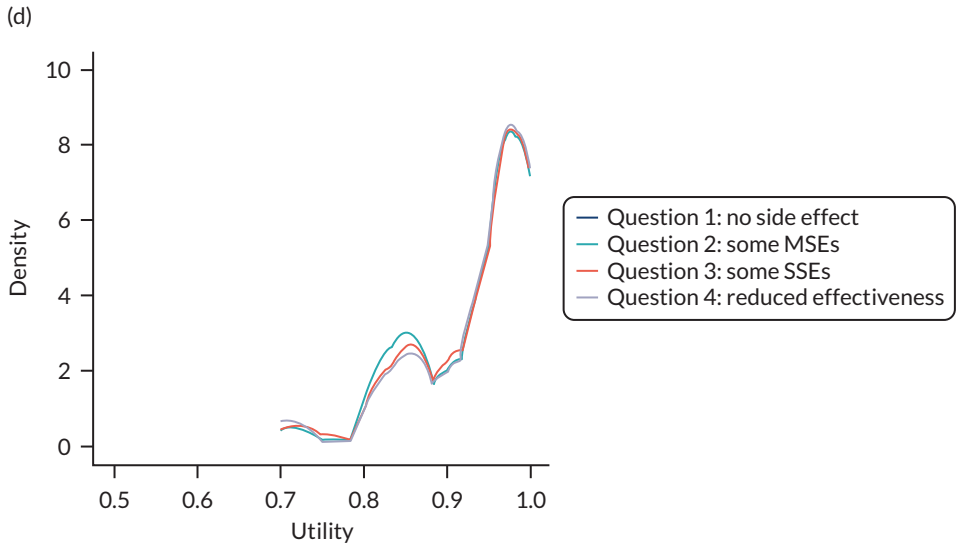


FIGURE 17 Kernel density plots showing distribution of TTO responses stratified by medicine, question context and respondent type. (a) Statin questions 1–4 utility values in patients; (b) statin questions 1–4 utility values in the public; (c) bisphosphonates questions 1–4 utility values in patients; and (d) bisphosphonates questions 1–4 utility values in the public.

a much lower DTD value than respondents who had no experience of daily medicine use. None of the other explanatory variables had a statistically significant association with DTD size, including the number of pills taken per day.

Best–worst scaling experiment

Analysis characteristics for respondents completing the BWS for statins (n = 319) and respondents completing the BWS for bisphosphonates (n = 312) are reported in *Table 12*. *Appendix 5*, *Table 46*, shows the count data [normalised based on the number of levels for each attribute: in/convenience (two levels), MSEs (four levels), SSEs (four levels)] for the number of times a respondent chose the attribute level as 'best' and 'worst', and the difference between 'best and worst'. *Appendix 5*, *Figures 34* and *35*, show the distribution of the count data for statins and bisphosphonates, respectively.

The data show that all the respondents had the strongest preference for taking a medicine with no inconvenience, which is the result expected a priori. This result was consistent between respondents with and without previous experience of taking a statin or bisphosphonate. The results from the pooled sample indicated that respondents had a strong dislike for experiencing the highest level of risk of a SSE. Overall, the respondents with experience of taking a statin or bisphosphonate indicated a greater dislike for a SSE and stronger preference for no inconvenience.

There was significant preference heterogeneity in the results. A fully correlated mixed logit model was, therefore, used to estimate preference weights for each attribute level relative to the reference level of 0.7% risk of a SSE (*Table 13*). The signs for all estimated coefficients in the fully correlated mixed logit model were consistent with a priori expectations based on the normalised best–worst scores. The estimated coefficients from the fully correlated mixed logit model were 're-scaled' by setting no inconvenience at a value of 1 and 0.7% risk of SSEs at zero to calculate an indicative utility score for no inconvenience. Using this approach, the DTD for a statin was 0.2 and 0.46 for a statin and bisphosphonate, respectively (i.e. compared with a life free of the medications, life lived with medications should be seen as 80% or 54% as desirable, respectively).

TABLE 11 Mean values and other summary statistics of DTD elicited using TTO

Medicine	Respondent	Question context	Mean	SD	Count	Skewness	Kurtosis	P1[a]	P25[a]	P50[a]	P75[a]	P90[a]	Proportion reporting disutility
Statins	Public	No side effects	0.965	0.057	237	−2.936	13.152	0.942	0.950	0.983	1.000	1	0.746
Statins	Public	Some MSEs	0.964	0.063	233	−3.344	17.003	0.942	0.950	0.995	1.000	1	0.721
Statins	Public	Some SSEs	0.964	0.060	232	−2.682	10.207	0.942	0.950	0.988	1.000	1	0.725
Statins	Public	Reduced effectiveness	0.964	0.063	232	−3.173	15.041	0.942	0.950	0.983	1.000	1	0.735
Statins in the public			0.964	0.061	934	−3.063	14.217	0.942	0.950	0.992	1.000	1	0.731
Statins	Patients	No side effects	0.974	0.054	161	−4.885	34.521	0.942	0.967	0.996	1.000	1	0.718
Statins	Patients	Some MSEs	0.972	0.056	156	−4.407	30.351	0.942	0.958	0.996	1.000	1	0.718
Statins	Patients	Some SSEs	0.968	0.060	150	−3.754	22.775	0.942	0.950	0.997	1.000	1	0.718
Statins	Patients	Reduced effectiveness	0.970	0.055	148	−2.768	10.985	0.942	0.950	0.997	1.000	1	0.714
Statins in patients			0.971	0.056	615	−3.971	24.829	0.942	0.967	0.997	1.000	1	0.717
Statins all respondents			0.967	0.059	1549	−3.379	17.681	0.942	0.950	0.995	1.000	1	0.725
Bisphosphonates	Public	No side effects	0.925	0.081	219	−1.312	4.800	0.833	0.850	0.967	0.989	1	0.860
Bisphosphonates	Public	Some MSEs	0.930	0.076	216	−1.213	3.825	0.833	0.883	0.967	0.992	1	0.846
Bisphosphonates	Public	Some SSEs	0.932	0.076	214	−1.319	4.205	0.833	0.883	0.967	0.996	1	0.846
Bisphosphonates	Public	Reduced effectiveness	0.933	0.078	216	−1.436	4.475	0.833	0.883	0.967	0.996	1	0.842
Bisphosphonates in the public			0.930	0.078	865	−1.325	4.382	0.833	0.883	0.967	0.995	1	0.849
Bisphosphonates	Patients	No side effects	0.949	0.069	42	−1.136	2.792	0.833	0.900	0.983	1.000	1	0.814
Bisphosphonates	Patients	Some MSEs	0.955	0.055	40	−0.977	2.551	0.867	0.917	0.967	1.000	1	0.826
Bisphosphonates	Patients	Some SSEs	0.958	0.060	40	−1.695	5.311	0.867	0.950	0.975	1.000	1	0.802
Bisphosphonates	Patients	Reduced effectiveness	0.956	0.065	39	−2.059	7.568	0.850	0.933	0.967	1.000	1	0.802
Bisphosphonates in patients			0.954	0.062	161	−1.506	4.694	0.850	0.933	0.967	1.000	1	0.811
Bisphosphonates all respondents			0.934	0.076	1026	−1.369	4.532	0.833	0.883	0.967	0.998	1	0.840
All statins and bisphosphonates			0.954	0.068	2575	−2.243	8.926	0.833	0.942	0.975	1.000	1	0.773

SD, standard deviation.
a P10 = 10th percentile, etc. Statins and bisphosphonates are means based across four subgroups listed.

TABLE 12 Description of the sample characteristics for BWS

Characteristic	Statin survey[a]			Bisphosphonate survey[a]			Total (*n* = 631)
	Experience of taking statin (*n* = 105)	No experience of taking statin (*n* = 214)	Total (*n* = 319)	Experience of taking bisphosphonate (*n* = 83)	No experience of taking bisphosphonate (*n* = 229)	Total (*n* = 312)	
Age (years), *n* (%)							
< 35	4 (3.81)	19 (8.88)	23 (7.21)	7 (8.43)	19 (8.3)	26 (8.33)	49 (7.8)
35–44	17 (16.19)	54 (25.23)	71 (22.26)	10 (12.05)	36 (15.72)	46 (14.74)	117 (18.5)
45–54	13 (12.38)	39 (18.22)	52 (16.3)	6 (7.23)	34 (14.85)	40 (12.82)	92 (14.6)
55–64	24 (22.86)	67 (31.31)	91 (28.53)	23 (27.71)	44 (19.21)	67 (21.47)	158 (25.0)
65–74	38 (36.19)	29 (13.55)	67 (21)	23 (27.71)	76 (33.19)	99 (31.73)	166 (26.3)
≥ 75	9 (8.57)	6 (2.8)	15 (4.7)	14 (16.87)	20 (8.73)	34 (10.9)	49 (7.8)
Sex, *n* (%)							
Female	48 (45.71)	153 (71.5)	201 (63.01)	71 (85.54)	186 (81.22)	257 (82.37)	458 (72.6)
Male	57 (54.29)	61 (28.50)	118 (37.0)	12 (14.46)	43 (18.78)	55 (17.63)	173 (27.4)
Ethnicity, *n* (%)							
White British/Irish	100 (95.24)	183 (85.51)	283 (88.71)	78 (93.98)	203 (88.65)	281 (90.06)	564 (89.4)
White other	0 (0.00)	13 (6.07)	13 (4.08)	3 (3.61)	11 (4.8)	14 (4.49)	27 (4.3)
Mixed/multiple ethnic origins	0 (0.00)	1 (0.47)	1 (0.31)	0 (0.00)	2 (0.87)	2 (0.64)	3 (0.5)
Black/African/ Caribbean/Black British	0 (0.00)	4 (1.87)	4 (1.25)	0 (0.00)	2 (0.87)	2 (0.64)	6 (1.0)
Asian/Asian British	3 (2.86)	10 (4.67)	13 (4.08)	1 (1.2)	8 (3.49)	9 (2.88)	22 (3.5)
Other ethnicity	2 (1.9)	3 (1.4)	5 (1.57)	1 (1.2)	3 (1.31)	4 (1.28)	9 (1.4)

continued

TABLE 12 Description of the sample characteristics for BWS (*continued*)

Characteristic	Statin survey[a]			Bisphosphonate survey[a]			Total (*n* = 631)
	Experience of taking statin (*n* = 105)	No experience of taking statin (*n* = 214)	Total (*n* = 319)	Experience of taking bisphosphonate (*n* = 83)	No experience of taking bisphosphonate (*n* = 229)	Total (*n* = 312)	
Number of pills taken daily, *n* (%)							
0	6 (5.71)	104 (48.6)	110 (34.48)	7 (8.43)	86 (37.55)	93 (29.81)	203 (32.2)
1	21 (20)	52 (24.3)	73 (22.88)	14 (16.87)	30 (13.1)	44 (14.1)	117 (18.5)
2–5	54 (51.43)	50 (23.36)	104 (32.6)	40 (48.19)	85 (37.12)	125 (40.06)	229 (36.3)
6–10	18 (17.14)	6 (2.8)	24 (7.52)	19 (22.89)	21 (9.17)	40 (12.82)	64 (10.1)
> 10	6 (5.71)	2 (0.93)	8 (2.51)	3 (3.61)	7 (3.06)	10 (3.21)	18 (2.9)
Number of different times pill taken per day, *n* (%)							
None	6 (5.71)	109 (50.93)	115 (36.05)	7 (8.43)	86 (37.55)	93 (29.81)	208 (33.0)
Once per day	38 (36.19)	64 (29.91)	102 (31.97)	23 (27.71)	62 (27.07)	85 (27.24)	187 (29.6)
Two times a day	41 (39.05)	26 (12.15)	67 (21)	35 (42.17)	59 (25.76)	94 (30.13)	161 (25.5)
Three times a day	12 (11.43)	7 (3.27)	19 (5.96)	16 (19.28)	15 (6.55)	31 (9.94)	50 (7.9)
More than three times a day	8 (7.62)	8 (3.74)	16 (5.02)	2 (2.41)	7 (3.06)	9 (2.88)	25 (4.0)
Mean (SD) EQ-5D-3L utility[b]	0.73 (0.34)	0.80 (0.24)	0.78 (0.28)	0.72 (0.26)	0.79 (0.24)	0.77 (0.25)	0.78 (0.23)

SD, standard deviation.
a Includes both patients recruited from GPs and public sample recruited from Dynata.
b Health status measured using the EQ-5D-3L and transformed into a utility score using Dolan.[116]

TABLE 13 Correlated mixed logit results for statin sample

	Bisphosphonates						Statins					
	With experience		Without experience		Pooled		With experience		Without experience		Pooled	
Attribute level	Coefficient	SE	Coefficient	SE	Coefficient	SE	Coefficient	SE	Coefficient	SE	Coefficient	SE
No inconvenience	5.232**	0.50	4.445**	0.30	3.675**	0.22	1.907**	0.29	2.700**	0.24	2.850**	0.22
Inconvenience	2.814**	0.36	2.515**	0.23	1.950**	0.20	1.457**	0.30	2.037**	0.22	2.064**	0.18
MSE												
1%	1.383**	0.29	1.898**	0.22	1.411**	0.16	1.147**	0.28	1.236**	0.17	1.498**	0.17
5%	1.208**	0.29	1.113**	0.23	0.707**	0.17	0.385	0.29	0.606**	0.17	0.865**	0.18
9%	0.921*	0.29	0.695*	0.24	0.275	0.18	0.246	0.29	0.037	0.19	0.546*	0.19
13%	0.871*	0.30	0.130	0.24	−0.094	0.19	0.152	0.30	−0.185	0.19	0.310	0.19
SSE												
0.1%	−0.359	0.41	0.540*	0.20	0.176	0.16	0.561	0.30	0.824**	0.21	0.777**	0.17
0.3%	−1.553*	0.50	0.265	0.24	0.019	0.17	−0.134	0.31	0.155	0.19	0.264	0.16
0.5%	−1.713*	0.55	0.181	0.22	−0.103	0.17	−0.372	0.30	−0.137	0.20	0.012	0.16
0.7%	3.625	N/A	−0.986	N/A	−0.092	N/A	−0.055	N/A	−0.843	N/A	−1.052	N/A
Number of observations	3320		9160		12,480		4200		8560		12,760	
Log-likelihood	−655.22		−2035.81		−2698.81		−926.252		−2001.62		−2985.87	
BIC	1748.26		4564.23		5906.94		2303.017		4492.20		6482.264	

* $p < 0.01$, ** $p < 0.001$.
BIC, Bayesian information criterion; N/A, not applicable.

Discussion

In this study, using the TTO method, we find that long-term statin use is associated with a DTD of 0.034 among people willing to take statins. We find that bisphosphonate use is associated with a DTD of 0.067 among people willing to take bisphosphonates. These values imply that, even if medicines have no specific adverse effects, the act of taking medicines can have a non-trivial effect on people's quality of life. We found no difference between patient and public disutilities for statins, but we did find that bisphosphonate patients generated smaller disutility values than the values coming from the general public.

Although we find that DTD values do not tend to differ based on the reported characteristics of the respondents in our survey, we do still find large variations across individuals. In line with previous empirical studies,[47,48,103] we find strong evidence for three different groups or types of respondent: (1) some never trading, suggesting zero disutility associated with treatments, (2) some always selecting the lowest possible value, suggesting that they would be unlikely to initiate treatment and (3) some willing to trade length of life for no ongoing treatment, suggesting a DTD. In our survey, the groups willing to trade and generate a DTD made up the majority of respondents surveyed, with approximately 72% and 84% for statins and bisphosphonates respondents, respectively.

The findings from the BWS experiment had face validity in that no inconvenience was the most preferred attribute. Inconvenience was a stronger driver of what to avoid when taking a medicine, but avoiding side effects were more important. The estimated values for DTD did not, however, have face validity. The DTD values were very large. This result is probably because the design of a BWS experiment that includes only the attributes of interest would tend to inflate the importance of inconvenience. Further analysis is planned to explore the effect of adjusting the observed DTD from the BWS with results from a TTO experiment that was embedded in the BWS survey.

Our research shows that people will trade life expectancy to avoid treatment characteristics in exactly the same way they will trade like expectancy to avoid undesirable health states. However, even though the preferences can be measured on the same scale, whether or not these two types of preferences should be treated as tradeable with each other is a normative question (i.e. should the NHS be paying for patients' convenience?) In England, at least, NICE appears to answer that question in the affirmative, stating that 'If characteristics of healthcare technologies have a value to people independent of any direct effect on health, the nature of these characteristics should be clearly explained and if possible **the value of the additional benefit should be quantified**. These characteristics may include convenience and the level of information available for patients' (emphasis added in bold; © NICE 2013 Guide to the Methods of Technology Appraisal 2013. Available from http://web.archive.org/web/20230117104032/https://www.nice.org.uk/process/pmg9/chapter/the-reference-case. All rights reserved. Subject to Notice of rights).[117] As far as we are aware, NICE has taken account of such factors only when it helps to differentiate one mode of treatment from another. For example, NICE Technology Appraisal 606,[118] considered subcutaneous compared with intravenous administration of medicines for hereditary angioedema, and the economic modelling in NICE Guideline 17[119] incorporated the benefit of continuous blood glucose monitoring compared with fingerprick tests. In both cases, the evidence relied on used methods that are comparable with our approach (i.e. TTO in members of the UK general population).[120,121] We see no reason why the process characteristics of some treatment compared with none should not be considered in the same way.

Nevertheless, the implications of our findings for future cost–utility analyses evaluating treatment pathways featuring statins or bisphosphonates (and potentially other oral medicines) are not straightforward. On the one hand, CEAs should ideally capture the impact of all relevant costs and consequences associated with alternative forms of treatment,[122] and so it must be relevant that we have demonstrated that the average person anticipates the act of taking statins or bisphosphonates will have a non-trivial impact on their quality of life. Accounting for this disutility is likely to reduce the desirability of treatments that are currently considered very cost-effective, and estimates of cost-effectiveness for

long-term preventative interventions have been shown to be particularly sensitive to the inclusion of DTD.[40,44,47,48,103,107,108,123,124] Indeed, we have previously shown that for some people for whom guidelines currently recommend statins (e.g. people at a 10% risk of a cardiovascular event over 10 years), a DTD that appears moderate in the light of the current study (0.015) would result in treatment doing more harm than good.[41]

On the other hand, the apparent existence of distinct preference groups among our respondents requires careful consideration. A substantial minority of participants repeatedly indicated that they would be unwilling to trade any life expectancy to avoid taking these medicines, suggesting that participants consider any inconvenience with which they are associated negligible. It would be difficult to deny access to a treatment on the grounds that the average person would be bothered by its process characteristics, which is a danger if population-level cost-effectiveness estimates routinely incorporate average DTD.

In view of these conflicting considerations, we recommend that decision-makers review scenarios with and without DTD. If evidence suggests that including DTD would materially alter the balance of benefits, harms and costs associated with treatment, then this should be highlighted in population-level guidance, enabling prescribers at an individual level to engage in shared decision-making that gives appropriate weight to the person's preferences for avoiding the treatment's process characteristics. Such an approach fits well with the guideline development methods for NICE,[125] which encourage the explicit identification of 'preference-sensitive decision points', taking the practicalities of possible treatments into account.

An alternative approach – broadly reflecting current practice – is to prescribe regardless of DTD and allow each person's emergent level of inconvenience define whether or not they adhere to the therapy. We believe that incorporating anticipated preferences in prospective shared decision-making is a superior approach, as it allows for an informed discussion of pros and cons and enables prescribers to tailor the strength of their advice accordingly. This should have the consequence that people whose expected benefits easily outweigh their short-term inconvenience will be less likely to discontinue treatments, whereas others who can expect only marginal gain will be less likely slavishly to adhere to a course of action that impairs their quality of life just because their doctor appeared to recommend it. Similarly, given that the emphasis of treatment decision-making now emphasises 'concordance' (i.e. agreement) rather than 'compliance' by the patient with clinical recommendations, better understanding that an individual's preferences around medicine-taking can influence whether or not net benefit is expected may lead to less potential conflict between prescribers and patients.

Limitations

There are some limitations to our study that need to be considered. Although we endeavoured to communicate complex concepts clearly within the study, this had a set of clear trade-offs for participants. The length of the survey, the cognitive burden and the time required to complete the survey were noted as challenges. Some of our respondents reported that they had difficulty understanding the TTO methods, whereas others provided inconsistent values across the survey questions. In addition, participants who took part in our survey ultimately self-selected and this could be related to their ability to complete the survey, as well as their self-reported health. Applicability for a different patient or general population should be made based on a careful judgement of the self-reported characteristics summarised for this study cohort.

It is not immediately clear which values elicited for DTD should be used. In terms of face validity, the DTD elicited from the TTO seemed 'better'. For the decision-analytic modelling reported in *Chapters 6* and *7*, we used the DTD values from the TTO study. This decision was made because the TTO method is consistent with how utility values are typically elicited to attach to health states in CEA.[117]

Conclusion

This study indicated that DTD does exist. It is not clear whether or not the DTD elicited from the TTO or BWS should be used; however, using face validity would suggest that the TTO method produced more realistic DTD values. We suggest that DTD should be included in model-based CEA of long-term preventative medicines, and *Chapters 6* and *7* explore the impact of using the elicited DTD values from the TTO method.

Chapter 6 Cost-effectiveness analysis accounting for competing risks and direct treatment disutility: statins for the primary prevention of cardiovascular disease

Background

Preventative treatments are different from interventions for acute conditions. Preventative treatments may have both immediate and persistent harms, but their benefits are deferred. It follows that shared decision-making between the patient and clinician about whether or not to start a preventative treatment should focus on whether or not the (potential) long-term health benefits are sufficient to justify the (certain) immediate burden and (possible) immediate or delayed harms. Clinical practice guidelines may provide recommendations, indicating whether or not this trade-off is positive for an average person. In England, at least, the developers of such guidelines are often informed by a quantitative analysis exploring the benefits, harms and costs of treatments compared with each other or with no treatment. This usually takes the form of a decision-analytic model that quantifies the net effects of competing approaches in terms of QALYs, encompassing expected benefits and harms, and compares these with net costs. Interventions will typically receive positive recommendations only if the guideline developers are confident that offering the treatment in question will result in population-level QALY gain (without imposing opportunity costs that imply even greater QALY loss in the wider health system). Therefore, prescribers may assume that, all things being equal, the preventative treatments that are recommended in trustworthy guidelines provide net benefit, and this seems like helpful information until one acknowledges that, in practice, all things never are equal.

Two particular dimensions in which any given person will diverge from population average are their clinical characteristics – especially with regard to long-term conditions other than the one of interest – and their preferences – in terms of whether or not they perceive a treatment is worth taking. Clinical guidelines often neglect to consider these factors, except in nebulous terms (e.g. encouraging prescribers to consider individualised risks and benefits, without providing any objective basis on which to introduce them to an options talk).

In the cost-effectiveness sections of this project, reported in this chapter and in *Chapter 7*, we aim to address this gap. We explore how accounting for clinical characteristics and preferences (accounted for using DTD) could alter the balance of benefits, harms and costs of preventative interventions. By adapting current methods used to populate model-based CEA of preventative medicines, we can better reflect the potential for subgroups of the patient populations to accrue different degrees of net benefit.

Our first objective is to tailor estimates according to competing mortality risk. As explored in *Chapters 2–4*, all people at risk of a given health condition are also at risk of other events that preclude the incidence of the condition of interest (unrelated death is an obvious example in almost all cases). We will see that, unlike epidemiological risk prediction models, decision-analytic economic models usually have some structural way of accounting for such competing events. However, decision modellers seldom pay close attention to how the likelihood of competing events is parameterised. Often, for example, decision modellers use an unadjusted estimate of general population mortality to reflect deaths that are not related to the condition of primary interest. We wanted to assess how much a failure to handle competing risks robustly might bias model outputs. This chapter explores an example using a cohort-level state-transition model (i.e. statins for the primary prevention of CVD) and *Chapter 7* looks at a patient-level discrete-event simulation (i.e. bisphosphonates for the primary prevention of osteoporotic

fragility fracture). In both cases, we build on the models that were used to underpin national guidance from NICE. In the case of statins, we use the model developed for Clinical Guideline 181 (CG181).[10] For bisphosphonates, we start from the model for Technology Appraisal 464 (TA464).[12] We do not necessarily assert that these are the best possible models in each decision space, and our choice to adopt and adapt the models arises from our interest in the extent to which existing population-level guidance might be affected by the issues under consideration.

Our second objective is to incorporate the evidence regarding DTD generated in *Chapter 5*, using the TTO method into modelled estimates of the cost-effectiveness of statins and bisphosphonates. Having found that a majority of people would be prepared to trade some of their life expectancy to avoid the inconvenience of taking statins or bisphosphonates, it is an obvious next step to ask whether or not the benefits of the interventions are sufficient to counterbalance this level of disutility. By integrating existing evidence with our new findings, we can derive QALY estimates for preventative medicines, compared with no intervention, that help us weigh up the overall balance of options for people with different levels of preference to avoid medicines.

Modifying existing methods in these ways allows us to define cost-effective subgroups of people who reflect different levels of competing risk (defined by specified levels of competing risk at different levels of baseline risk) and different degrees of DTD (defined by specified levels/durations of DTD).

Methods

We used a cohort-based decision-analytic model to address the stated decision problem (*Table 14*).

TABLE 14 Key design criteria for decision-analytic model for statins for primary prevention of CVD

Decision-analytic model	Criterion
Decision problem	What is the impact of including competing risk in a risk prediction algorithm to inform whether or not to start a statin in a population at risk of events as a result of CVD?
Intervention	Statins at three different intensities: low (simvastatin 10 mg/day), medium (simvastatin 20 mg/day) and high (atorvastatin 20 mg/day)
Comparators	No treatment
Model type	State-transition Markov model
Population	Men and women of any age potentially eligible for a statin based on QRISK3 10-year predicted risk of incident CVD
Setting	Primary care services in NHS England
Time horizon	40 years
Study perspective	NHS in England
Costs	Statins
	Treating subsequent CVD-related events
	Measured using GBP (£) at 2019–20 prices
Consequences	Impact on health status (± DTD) measured using QALYs
Discounting	3.5% for costs and consequences
Cost-effectiveness threshold	NICE-recommended threshold of £20,000 per QALY gained

Selection of the statins case study

The decision-analytic model we adopted and developed for this decision problem takes a cohort-level state-transition (Markov) approach to predicting events of interest and estimating costs and effects.[10]

Decision-analytic models of this type account for competing risks by design. For example, consider a Markov model with the three states of (1) well, (2) myocardial infarction (MI) and (3) dead (for our purposes, we will define the latter two as absorbing states from which further transitions are not of interest) and let per-cycle transition probabilities $p_{well \rightarrow MI}$ and $p_{well \rightarrow dead}$ both be 0.1. Assuming the whole cohort starts in the well state, after one cycle of the model 10% of people will be in the dead state and 10% will be in the MI state, leaving 80% in the well state. Note that, via the transition to death, 10% of the people who were initially at risk of a MI have been taken out of the at-risk state before cycle 2 without experiencing a MI. After the second cycle, we will have 18% of the cohort in the MI state ($1 \times 0.1 + 0.8 \times 0.1$); however, if we had a two-state well MI model with no competing risk of death, then it would have been 19% ($1 \times 0.1 + 0.9 \times 0.1$). If we run the model on for 10 cycles, and we find that 44.6% of people have had a MI, then without the competing transition to death the number would be 65.1%.

This simple example demonstrates that a competing risk structure is hardwired into the kind of state-transition models that are very commonly used to assess the cost-effectiveness of healthcare interventions. The example also shows that, to parameterise any given transition within such a structure, it is appropriate to rely on evidence that censors for competing events. Were we to base our inputs on time-to-event models that, themselves, adjust for competing risks (e.g. models explored in *Chapters 2* and *3*), our model would underestimate the probability of events of interest, as we would be effectively double counting the competing risks.

Clearly, however, it is important that the time-to-event evidence on which a decision model relies should be valid for the population to which the decision problem pertains. It should be clear from the above that if we have an inappropriate estimate of any one of our transitions, then it is not only with respect to that outcome that our model will be biased, as it will also compromise our estimate of any events with which it competes.

In an epidemiological risk prediction model, failing to account for competing risks will result in an overestimate of event rates for the whole cohort. In a state-transition decision model, the danger is that we will fail to account accurately for competing risks, which will lead to overprediction of events in people with higher-than-average competing risk and underprediction of events in people with lower-than-average competing risks.

Model overview

Table 14 summarises the decision problem and scope of the analysis for the model-based CEA. The model from which we started directly replicates the model developed to inform decision-making about primary prevention of CVD in CG181.[10] The published guideline provides a detailed description of methods.[10]

In summary, the model takes a cohort-level state-transition (Markov) approach. The model has a 1-year cycle length and a 40-year time horizon. *Figure 18* illustrates the model structure. As the decision problem relates to primary prevention, the whole cohort starts in the 'no known CVD' state. As time progresses in the model, the model simulates a proportion of people experiencing one or more of seven distinct non-fatal cardiovascular events [i.e. stable angina (SA), unstable angina (UA), MI, stroke, TIA, peripheral arterial disease (PAD) and heart failure]. The model also accounts for cardiovascular death and other-cause mortality. For each of the non-fatal cardiovascular events, an initial 1-year cycle reflects an acute event or diagnosis and a post-event state reflects people living with a history of the event in subsequent years. Repeat acute events are possible for MI and stroke. Where evidence was available to the CG181 modellers, other secondary events occur from most acute and post-event states. However, in

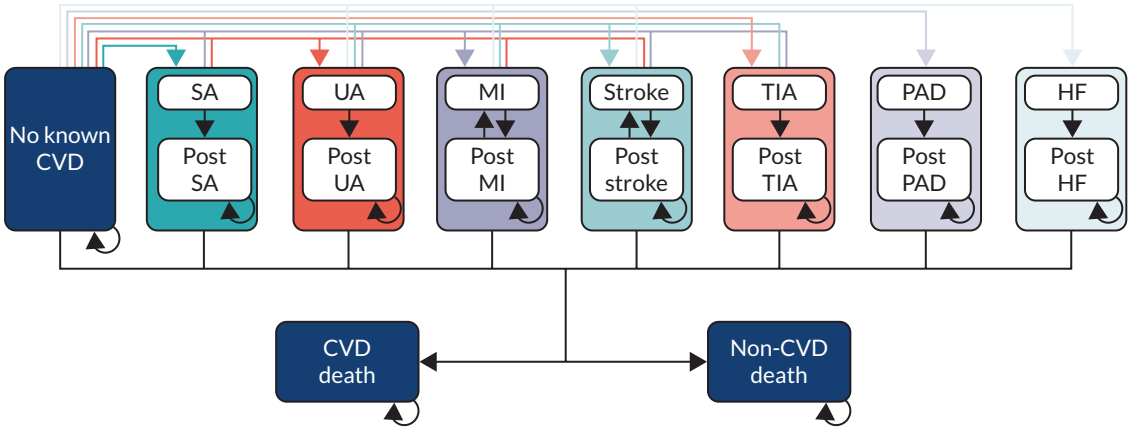


FIGURE 18 Structure of state-transition model assessing statins for primary prevention of CVD. HF, heart failure.

the base case, no further events are allowed from PAD and heart failure (as these events are associated with the highest probability of cardiovascular death, meaning that additional events would unrealistically confer an improvement in prognosis).

However, in the base case, no further events are allowed from PAD and heart failure (as these events are associated with the highest probability of cardiovascular death, meaning that additional events would unrealistically confer an improvement in prognosis).

The model simulates a cohort comprising men and/or women of a specified age and a baseline 10-year risk of a first cardiovascular event (i.e. events counted by QRISK3: SA, UA, MI, stroke, TIA and cardiovascular death). (Note that the model handles heart failure and PAD separately on the assumption that their incidence is proportional to that of the QRISK3 events.) Calculations are based on true baseline risk, that is, absent competing events, 20% of people with a 20% 10-year risk will experience a first cardiovascular event in the first 10 years of the model.

The ways in which we have adapted the model fall into two broad categories. First, there were 'general model updates' that reflect steps we took to bring the CG181 model up to date and improve the parameterisation and/or implementation of existing functionality. Second, we introduced new features to explore the issues of interest for this project (i.e. accounting for competing risk and the incorporating DTD).

General model updates

Except where otherwise described, our version of the model retains the inputs used for the CG181 analysis (see guideline documentation for full details[10]).

Natural history: mortality statistics

The CG181 model relied on ONS lifetables for England for 2010–2. We configured the model to simulate present-day life expectancy using ONS lifetables for 2017–9.[126] While we were in the latter stages of preparing this report, ONS lifetables for 2018–20 became available; however, we did not update the model to use these data, as the data include substantial excess mortality owing to the COVID-19 pandemic that began in 2020.

The model also needs an estimate of the proportion of deaths that are caused by CVD. For this estimate, the CG181 model used ONS death registration statistics for England and Wales from 2012, selecting all deaths recorded under ICD-10 codes I00–I99. For this study we did exactly the same, using data for 2019 that are now available through an ONS Application Programming Interface.[127]

Type of first cardiovascular event

In the CG181 model,[10] as preserved in our update, a cohort's cardiovascular risk is defined by its specified 10-year QRISK3 predicted risk. The model treats this value as deterministically exact, that is,

absent competing risks, 20% of a cohort with a 20% 10-year cardiovascular risk will experience a first qualifying event in the first 10 years of the model.

The model subdivides the proportion of people experiencing a first event into eight event-specific states. Six events were covered by QRISK3 (i.e. SA, UA, MI, stroke, TIA and cardiovascular death) plus two additional events (i.e. heart failure and PAD) (see *Figure 18*). In CG181, the evidence used to define the split came from the original NICE technology appraisal on statins,[128] which took data from a variety of sources.[129–131] This evidence is 25–40 years old and it does not account for underlying level of risk (i.e. it is plausible that people at low risk of cardiovascular events experience a different distribution of first events from people at high risk). Moreover, it is suboptimal to derive a subdivision like this using disparate sources of evidence. Therefore, we used the CPRD data set generated for the cardiovascular element of this project (see *Chapter 2*) to develop a new estimate of type of first cardiovascular event, conditional on some event having occurred. We fitted a multinomial logistic regression model to estimate the relative probabilities of a cardiovascular event being of each type, according to sex, age at event and baseline QRISK3 predicted risk. *Appendix 6* provides full methods, including a worked example calculation and resulting inputs for the decision-analytic model.

Increasing cardiovascular risk over time

The CG181 model incorporates a year-on-year linear increase in cardiovascular risk (0.3% per year for men and 0.08% per year for women), based on a regression undertaken for the original NICE technology appraisal on statins.[128] The model applies this yearly increment in the initial 10-year period, over which the user specifies baseline risk (centring the risk around the middle of the period so that the cumulative risk over the 10 years is very close to the specified level) and then extends the same linear increase beyond to the model's time horizon.

We retained the assumption that the increase is linear over the initial 10 years. However, beyond the period of fixed risk, we made use of evidence from the QRISK3 derivation study,[25] that is increase in cardiovascular risk accelerates as people get older. We configured the model to use the age coefficients from QRISK3 to estimate HRs for people as they age. For men, QRISK3 estimates age-related risk in terms of $(age/10)^{-1}$ and $(age/10)^{3}$, for which the log-HRs are −17.84 and 0.0023, respectively. For women, the parameters are $(age/10)^{-2}$ and $(age/10)$ and the log-HRs are −8.14 and 0.797, respectively. We verified that our implementation of these data exactly matches the 'HRs by age' depicted in supplementary material for the QRISK3 derivation paper.[25] Using this approach, our model calculates HRs for people as they age, compared with their risk at the end of the initial 10-year period, and applies the HRs to calculate yearly risk increases.

When performing this update, our study also identified an error in the CG181 model in how increasing baseline risk interacts with treatment effect,[10] as this leads to anomalous results where statins – despite being notionally subject to a constant relative risk indicating benefit – are associated with raised risk of some events (i.e. stroke and cardiovascular death) in later cycles of the model. A negative effect of statins also develops for heart failure, even though, in its base case, the CG181 model[10] and ours assume a relative risk of 1 (i.e. no benefit) for this outcome. We corrected this error in our implementation of the model.

Treatment effectiveness

We have not updated any estimates of the effectiveness of statins in preventing CVD and, therefore, these estimates remain as in CG181.[10] For high-intensity regimens, this means relative risks of 0.46 (95% CI 0.37 to 0.59) for MI, 0.80 (95% CI 0.70 to 0.91) for stroke and 0.73 (95% CI 0.61 to 0.88) for cardiovascular death. As in CG181,[10] we assume that statins' effect in reducing MI also applies to SA, UA and PAD, and that the effect for stroke applies to TIA. We do not model a benefit for statins in reducing incidence of heart failure.

The base-case model presented in CG181[10] included a benefit for statins in reducing non-cardiovascular mortality. The evidence supporting this assumption was weak in 2014, and we are not aware of any stronger data since the guideline was published. Therefore, we have removed this assumption from our base case (i.e. we do not model any non-cardiovascular benefit for statins).

Health-related quality of life: underlying

The developers of the model that informed the original NICE technology appraisal for statins[128] undertook a linear regression on patient-level data from the study reported by Kind *et al.*[132] to estimate baseline quality of life. This analysis, which the CG181 model subsequently adopted, uses data from the general population and defined utility as a function of age, without accounting for sex or any non-linear effects. We considered that it could be important to account for these factors in a more flexible way and so we undertook a new regression, using a pooled sample of respondents from the Health Survey for England (HSE)[133] (see *Appendix 6* for full details).

Health-related quality of life: cardiovascular events

To quality-adjust expected survival for cost–utility analysis of a state-transition model, we require estimates of the quality of life associated with each of the model states. We performed a systematic literature review to update the health state utility values from the CG181 model.[10] To identify estimates for each model state, we adopted a pragmatic approach, following recommendations in the NICE Decision Support Unit's technical support document for utility values.[134] *Appendix 6* provides details of the values we selected for the updated model and the process by which we identified and selected them. *Appendix 6*, *Table 51*, provides full details of the final inputs.

Adverse drug events

The CG181 model accounted for one adverse effect of statins, based on evidence appearing to show hastened onset of type 2 diabetes at the time.[10] However, a recent systematic review found no association between randomisation to statins and incidence of diabetes [odds ratio (OR) 1.01, 95% CI 0.88 to 1.16].[135] Therefore, we removed this feature from our version of the model.

The adverse event with which people most commonly believe statins are associated is muscle pain. However, it is hard to find objective evidence confirming a harm of meaningful magnitude in this domain. A recent comprehensive systematic review summarising the experience of over 65,000 trial participants found that statins are significantly associated with an increase in muscle symptoms, but the effect is extremely small, with 15 (95% CI 1 to 29) extra events per 10,000 patient-years.[135] Two UK-based randomised crossover trials that postdate the review found no difference in muscle symptoms between the phases when participants took statins and phases when participants received placebo.[43,136,137]

The meta-analysis also found very small increased risks of liver, kidney and eye problems with statins compared with controls, with increased incidences of 8, 12 and 14 events per 10,000 patient-years, respectively.[135] These events are all mild and, in the case of liver and kidney reports, largely based on laboratory findings rather than clinically overt symptoms.

Even if we were to assume that all these events were serious, their incidence is increased so little that including the events in a cost–utility analysis would make no material difference to results. For example, if we ascribe the substantial disutilities that have been reported for people living with chronic complaints affecting the same body parts [−0.212 for 'Other problems of bones/joints/muscles', −0.102 for 'Other digestive complaints' (including liver), −0.176 for 'Kidney complaints' and −0.114 for 'Cataract/poor eye sight/blindness'[138]] and assume each adverse event lasts for 1 month (except for eye problems, which we extend to a mean of 5 years to reflect the possibility of long-term harm), the net expected health loss across all these categories would total 0.0008 QALYs, which is equivalent to less than one-third of a day in perfect health. As this is a negligible amount, and almost certainly a substantial overestimate (as reported events are nowhere near as serious as those from which we obtained the utility decrements), we concluded that there would be no benefit in configuring our model to simulate adverse events.

Nevertheless, the fact that many people believe that statins cause harms is, in itself, a harm associated with statins. A recent crossover trial by Howard *et al.*[43] also included no-treatment periods along with

statin and placebo phases. Although there was no difference between statin and placebo periods, the level of self-reported muscle symptoms was significantly higher when participants took either pill than it was for the no-treatment phases, and this strongly suggests that statins have 'nocebo' effects. Howard *et al.*[43] conclude that 'It is clear that this cohort were indeed intolerant of statin tablets, but also that the source of the intolerance was primarily the tablet, not the statin'. We will argue below that our exploration of DTD provides a useful paradigm in which to conceptualise nocebo effects as an authentic harm of treatment.

Resource use and costs: acquisition of statins

We updated the acquisition costs of statins to present-day levels, using data from the NHS Drug Tariff (November 2021).[139] The new prices (per pack of 28 tablets) were £0.92 for simvastatin 10 mg (i.e. low intensity), £0.96 for simvastatin 20 mg (i.e. medium intensity), £1.10 for atorvastatin 20 mg (i.e. high intensity) and £1.68 for atorvastatin 80 mg (i.e. high intensity and secondary prevention).

Resource use and costs: cardiovascular events

In addition to the costs of the interventions modelled, the model requires annual per-person costs of NHS and Personal Social Services care associated with each state (in GBP and for the relevant price year) to calculate lifetime costs of CVD in each cohort. We updated all model inputs in this area on the basis of a rapid review we undertook using a pearl-growing approach based on two previously known sources (one for stroke/TIA[140] and one for cardiovascular events[141]). *Appendix 6* details our methods and shows the resulting model inputs.

New model features specific to this project

Accounting for competing risk of non-cardiovascular death

The CG181 model[10] accounts for background non-cardiovascular mortality using general population lifetables. A key motivation of this project (see *Background*) was to improve on this by ensuring that, for any modelled cohort, the competing risk of non-cardiovascular death reflects the life expectancy of people with the specified level of cardiovascular risk. Official lifetables stratify by age and sex; however, the lifetables do not tell us how all-cause mortality might be associated with cause-specific factors, such as cardiovascular risk. Therefore, we needed a method that will enable us, in effect, to estimate cardiovascular risk-specific non-cardiovascular lifetables.

To do this, we fitted a relative survival model to the cardiovascular CPRD data set used in the cardiovascular element of this project (see *Chapter 2*), using the multiplicative method of Andersen *et al.*[142] This approach is a variant of a Cox proportional hazards model that uses the life expectancy of a reference group (in this case, non-cardiovascular survival in the general population) as a time-varying covariate. For a formal definition of the model, see *Appendix 6*.

Our rationale for using a relative survival model is threefold. First, we needed some way of not only characterising observed survival in the CPRD data set (which has a median follow-up of 5 years), but also extrapolating to the lifetime horizon of the decision model. Decision-analytic economic models commonly use parametric models to accomplish this type of task; however, such models invariably characterise a discrete cohort of which we can plausibly assume that the members share a survival distribution (e.g. people with newly diagnosed cancer of a given type). In this case, we want to simulate heterogeneous groups of people (e.g. 40-year-old women with a 10-year cardiovascular risk of 2%; 80-year-old men with a 10-year cardiovascular risk of 40%) and it is implausible to assume that we can describe the expected survival of all such groups with a common parametric foundation. With a relative survival model, we do not need to define a functional form, we simply have to estimate a model that we can apply to a baseline drawn from empirical lifetable data, as this will naturally produce survival curves that vary in shape and scale, even though the relative difference between the general population and the modelled cohort is a constant function of the covariates. Second, we wanted an approach we could use to estimate the life expectancy of cohorts for whom the decision to initiate statins takes place in the

present day. Characterising the relative relationship between observed survival and expected population survival from contemporaneous lifetables provides us with a model we can then apply to present-day lifetables. In doing this, we make the assumption that, although absolute life expectancy may have changed over time, the extent to which factors of interest affect it generalise across time with minimal bias. Third, relative survival models provide a parsimonious way of summarising complex data. If, as discussed above, we relied on parametric models to extrapolate to lifetime expectation, then we would inevitably need to fit multiple models to discrete subsets of the data; however, if we had chosen too few, then we would have inappropriately lumped people with heterogeneous expectations together, and if we had chosen too many, then we would have generated high-variance estimates with a tendency to overfit to artefacts in uncertain data. In contrast, the relative survival approach enables us to make use of all available data while adjusting for the things that might define groups with different expectations. Another reasonable approach would have been to fit a multistate model to the CPRD data; however, this would not solve the problem of extrapolation beyond the observed evidence and may have given us less flexibility in simulating cohorts with different baseline characteristics and risk profiles.

The output of the relative survival model is the multiplicative difference in time to event (in our case, non-cardiovascular death) between a person in a specific population and someone of the same age and sex in the general population. The coefficients show how this difference varies with each covariate.

For our models, the critical covariate is ΔQ, which we define as the difference between an individual's predicted 10-year QRISK3 score and the average score for a person of the same age and sex. Because QRISK3 predicted risk is a probability it is bounded between 0 and 1 and, therefore, it becomes mathematically convenient to transform the estimates to a log-odds scale and so we work with $\Delta\text{logit}(Q)$. Because population lifetables do not provide information on QRISK3 scores we estimated average 10-year risks by age and sex using a regression on the CPRD data set (see *Appendix 6*, *Table 54* and *Figure 39*). Owing to computational constraints, we were unable to fit a single relative survival model to the whole CPRD extract and, therefore, we developed separate models for men and women.

To begin with, we fitted relative survival models with a single coefficient [i.e. $\Delta\text{logit}(Q)$].

As lifetables are already stratified by age, it is theoretically not necessary to include a term for it in a relative survival model. However, it is plausible that the effect of other covariates – in this case, $\Delta\text{logit}(Q)$ – varies with age. Therefore, we also fitted a more complicated model including age and its interaction with $\Delta\text{logit}(Q)$. At the same time, we explored introducing polynomial terms to account for non-linearity of effect. We found that using quadratic terms for both $\Delta\text{logit}(Q)$ and age improved the fit of the model (reducing AIC by several hundred points); however, the inclusion of higher-order polynomials provided diminishing returns. Therefore, the linear component of our more complex model takes the form:

$$\Delta\ \text{logit}\,(Q) + \ \Delta\ \text{logit}(Q)^2 + age + age^2 + \ \Delta\ \text{logit}\,(Q) \times age + \ \Delta\ \text{logit}(Q)^2 \times age + \ \Delta\ \text{logit}\,(Q) \times age^2 + \Delta\ \text{logit}(Q)^2 \times age^2. \quad (1)$$

Table 15 shows the results of simple and polynomial models fitted for men and women separately.

To give a worked example, consider a 60-year-old man with a 10-year QRISK3 predicted CVD risk of 20%. First, using *Appendix 6*, *Table 54*, we calculate the average logit(QRISK3) for a person with those characteristics:

$$12.90 + 0.353 \times 60 - 5.60 \times 10^{-3} \times 60^2 + 6.31 \times 10^{-5} \times 60^3 - 4.18 \times 10^{-7} \times 60^4 + 1.42 \times 0^{-9} \times 60^5 - 11.02 + 0.986 \times 60 + 0.0320 \times 60^2 + 5.20 \times 10^{-4} \times 60^3 - 4.28 \times 10^{-6} \times 60^4 + 1.41 \times 10^{-8} \times 60^5 = -1.815. \quad (2)$$

TABLE 15 Relative survival models: non-cardiovascular mortality as a function of predicted cardiovascular risk and age in men and women

Parameter	Simple model, HR (95% CI)	Polynomial model, HR (95% CI)
Men		
Δlogit(Q)	1.9314 (1.8747 to 1.9898)	2.7540 (2.5997 to 2.9174)
$\Delta\text{logit}(Q)^2$	–	0.8787 (0.8336 to 0.9262)
Age	–	1.0111 (1.0090 to 1.0133)
Age^2	–	0.9998 (0.9998 to 0.9999)
Δlogit(Q) × age	–	1.0229 (1.0183 to 1.0275)
$\Delta\text{logit}(Q)^2 \times \text{age}$	–	0.9858 (0.9833 to 0.9883)
$\Delta\text{logit}(Q) \times \text{age}^2$	–	0.9989 (0.9987 to 0.9990)
$\Delta\text{logit}(Q)^2 \times \text{age}^2$	–	1.0001 (1.0000 to 1.0003)
AIC	518,564	517,989
Women		
Δlogit(Q)	1.7061 (1.6789 to 1.7338)	2.2100 (2.0959 to 2.3304)
$\Delta\text{logit}(Q)^2$	–	0.9809 (0.9473 to 1.0158)
Age	–	0.9978 (0.9954 to 1.0001)
Age^2	–	1.0002 (1.0001 to 1.0002)
Δlogit(Q) × age	–	1.0235 (1.0190 to 1.0281)
$\Delta\text{logit}(Q)^2 \times \text{age}$	–	0.9918 (0.9899 to 0.9938)
$\Delta\text{logit}(Q) \times \text{age}^2$	–	0.9994 (0.9992 to 0.9995)
$\Delta\text{logit}(Q)^2 \times \text{age}^2$	–	0.9999 (0.9998 to 1.0000)
AIC	536,994	536,427

On a probability scale, this is a 10-year risk of 14% (i.e. our hypothetical man is subject to higher-than-average risk). Next, we calculate Δlogit(Q), that is the difference between observed and expected risk, and in this case it is logit(0.2) minus −1.815 = 0.429. Plugging this value into our polynomial model gives:

$$1.013 \times 0.429 - 0.129 \times 0.429^2 + 0.01106 \times 14.57 - 0.000176 \times 14.57^2 + 0.02262 \times 0.429 \times 14.57 - 0.014348 \times 0.429^2 \times 14.57 - 0.001134 \times 0.429 \times 14.57^2 + 0.00014 \times 0.429^2 \times 14.57^2 = 0.540. \quad (3)$$

(Note that for summation we use the natural logarithm of the coefficients given in *Table 15* and age is centred around the population mean of 45.43. Therefore, in this case, 60 – 45.43 = 14.57.)

When exponentiated, this value provides a HR of 1.72. Therefore, we estimate that a 60-year-old man with a 10-year QRISK3-predicted CVD risk of 20% is, alongside his raised cardiovascular risk, subject to a hazard of non-cardiovascular death that is more than two-thirds higher than that of an average person of that age and sex. This is the value that we apply to general population lifetables (adjusted to remove cardiovascular deaths) when we simulate the non-cardiovascular life expectancy of a cohort with those characteristics.

Figure 19 shows estimates of non-cardiovascular mortality generated in the way described above, compared with empirical data across different categories of cardiovascular risk and age. The empirical Kaplan–Meier curves represent observed non-cardiovascular mortality (censored for cardiovascular

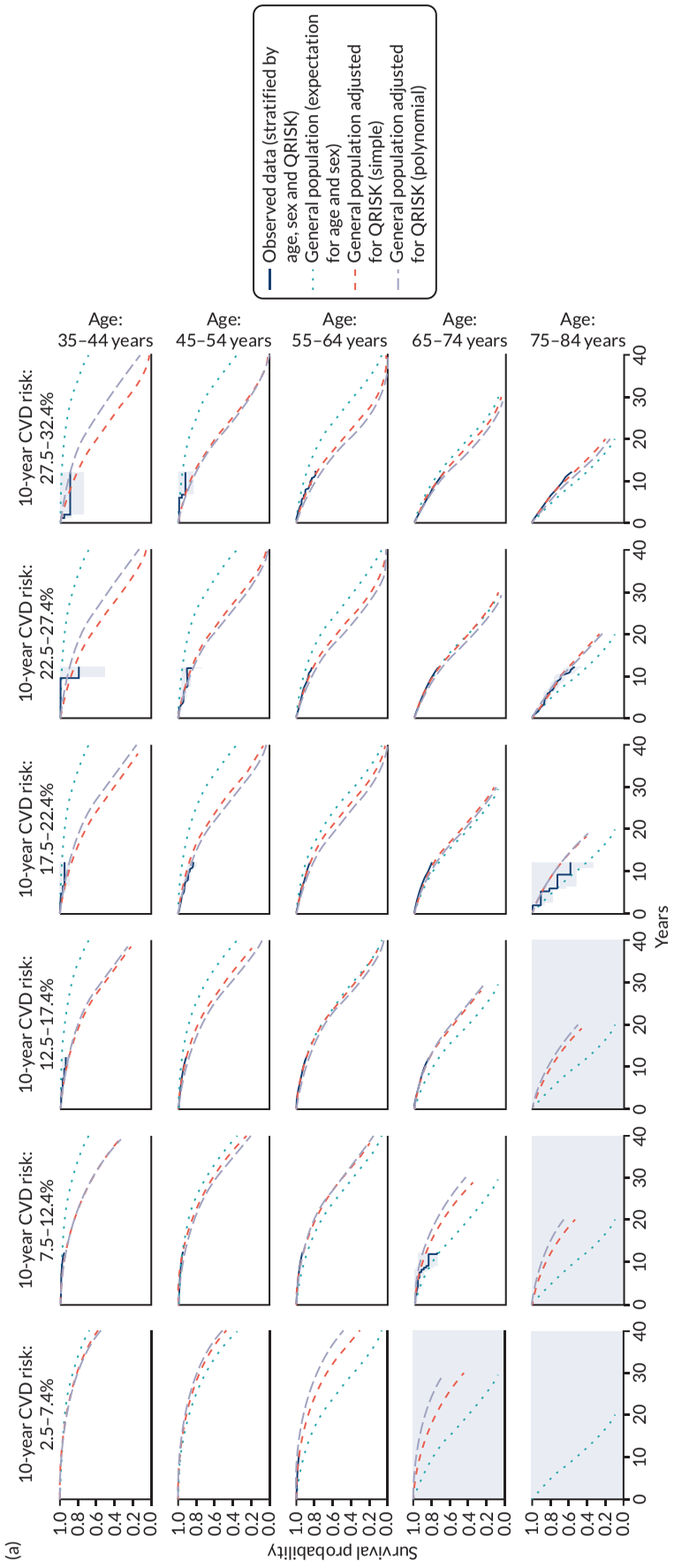


FIGURE 19 Fitted relative survival models for non-cardiovascular mortality compared with empirical data. (a) Men; and (b) women. (*continued*)

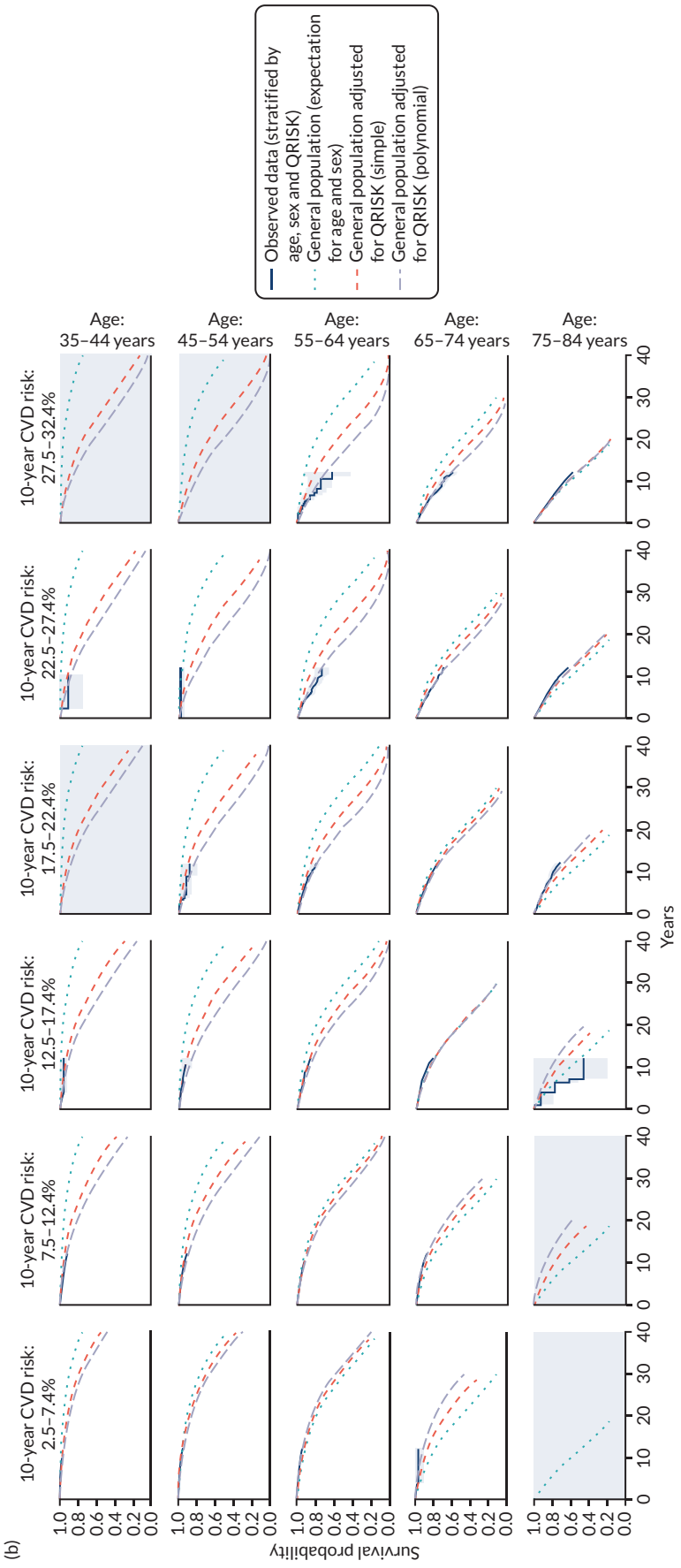


FIGURE 19 Fitted relative survival models for non-cardiovascular mortality compared with empirical data. (a) Men; and (b) women.

death) in the CPRD extract for people of the stated age, with baseline QRISK3 predictions in the specified brackets. For our modelled estimates, we start from ONS 3-year lifetables for England and Wales (for this illustration we use 2009–11 tables, as this is in the middle of the period covered by the CPRD data). We adjust these data to remove cardiovascular deaths, estimated using proportions recorded under ICD-10 codes I00–I99 in ONS's 'Deaths registered in England and Wales' series. For each combination of risk and age bracket, we calculate HRs, as described above (for comparability, we fit at the mean QRISK3 prediction and age observed within that category in the CPRD data), and apply the HRs to the ONS curves, and this produces the adjusted curves shown in *Figure 19*.

This exercise shows that the approach produces an excellent fit to the observed data. Even though the simple models (i.e. short dash) depend on a single variable, the simple models capture most of the observed variability in non-cardiovascular death. The polynomial models with age interactions (i.e. long dash) improve this fit somewhat further, at least falling within the 95% confidence limits of the observed survival functions in almost all cases. (One exception is 45- to 54-year-old women with a 10-year QRISK3 CVD prediction of 25% ± 2.5%, as these women appear to have better survival than women of the same age with lower cardiovascular risk; however, we consider this an implausible artefact of the relatively small sample of women in the category.)

Note that within each age bracket the unadjusted general population estimate (see *Figure 19*) remains the same across cardiovascular risk categories. Estimating competing-cause mortality on the basis of age and sex alone, without accounting for the way in which it correlates with the risk of interest, is the approach the CG181 model takes,[10] but this analysis shows that such an approach can misestimate competing mortality risk to a potentially substantial degree.

For example, for women aged 65–74 years the unadjusted general population estimate suggests that women of this age have around an 84% chance of surviving 10 years without experiencing non-cardiovascular death. However, if a woman in this category had a predicted cardiovascular risk between 7.5% and 12.4%, then she would be uncommonly healthy and so her true 10-year non-cardiovascular survival would be around 91%. Conversely, if a woman had a high QRISK3-predicted risk of the order 27.5%–32.4%, then she would have below-average health and her 10-year non-cardiovascular survival probability would be around only 70%. In the former case, a model relying on unadjusted competing-cause mortality estimates would underestimate likely survival by a non-trivial amount. In the latter case, the bias is reversed. Note that in both cases the unadjusted population expectation is not within the confidence limits of the observed Kaplan–Meier estimate, whereas our adjusted estimates pass closely through them.

Incorporating direct treatment disutility

The TTO exercise we conducted as part of this project (see *Chapter 5*) established that most respondents would be prepared to sacrifice an amount of life expectancy to avoid the inconvenience of taking statins to prevent CVD. Across all participants, the average estimated utility was 0.966 (95% CI 0.961 to 0.971). Note that, as explained in *Chapter 5*, we exclude participants who would trade 50% of their life expectancy to avoid taking statins, as we take the view that people with such marked preferences are not relevant to the decision problem of whether or not to offer statins for primary prevention of CVD because they would always decline.

We explore the effect of including DTD at this level on the outputs of our model in four scenarios:

1. No DTD (i.e. as per CG181[10]).
2. Permanent DTD (i.e. disutility of the specified level throughout the time simulated patients are taking statins for primary prevention of CVD).
3. Time-limited DTD (i.e. disutility of the specified level for a given number of model cycles and we start by assuming that DTD lasts for 10 years, although we explore this value further).
4. Diminishing DTD (i.e. a linear decline in disutility from the specified level to zero over a given number of cycles and, again, we start from 10 years and explore further).

In our base-case analyses, we apply DTD multiplicatively (e.g. a multiplier of 0.966) and we test the model's sensitivity to this assumption in additional scenarios in which we assume an absolute effect (e.g. a decrement of 0.034).

We do not apply DTD to states representing cardiovascular events and post-event life. Although the model assumes that people will take statins in these states and includes a cost for them, our elicitation exercise was explicitly focused on the use of statins for primary prevention in people with no cardiovascular history, and it is not clear that people would make similar trade-offs when it comes to statins for secondary prevention. It would also be difficult to apply any time-dependent DTD for secondary prevention in our model, as it has a 'memoryless' Markov structure, with a proportion of people experiencing first cardiovascular events at every cycle.

Model verification

Before making any updates or amendments, we verified that our version of the model exactly reproduced reported results from CG181.[10] We also performed technical verification to confirm that the model results changed in the expected direction when extreme values were used for specific model inputs.

Base-case analysis

Clinical Guideline 181[10] presented cost–utility results for no preventative treatment and for statins at three levels of intensity (i.e. low, medium and high). All of the statin arms assumed class-level effects and used the acquisition costs of a single representative drug (i.e. simvastatin 10 mg/day, simvastatin 20 mg/day and atorvastatin 20 mg/day for low-, medium- and high-intensity therapy, respectively). An additional arm used identical effects to the high-intensity arm, but adopted the costs of atorvastatin 80 mg/day. Therefore, there were five arms in total.

Our model retains these five arms, and full incremental results are presented in *Appendices 7* and *8*. However, to simplify interpretation, the main analyses presented below focus on a pairwise comparison between high-intensity therapy with atorvastatin 20 mg/day and no treatment, as this is the approach the guideline ultimately recommended.

Sensitivity analyses

We use three types of sensitivity analyses (i.e. probabilistic sensitivity analysis based on 1000 iterations per output set, deterministic one-way sensitivity analysis and scenario analyses) to look at the impact of different assumptions about DTD.

Results

General model updates

Before accounting for competing risks or DTD, in *Table 16* we break down the independent and cumulative impact of each of the steps detailed in General model updates (above). The updates with the largest impact serve to improve the estimated cost-effectiveness of statins. Correcting the miscalculation by which statins were erroneously associated with increased incidence of some cardiovascular effects has the largest effect and, unsurprisingly, this increases the incremental QALYs conferred by statins and reduces their net costs. Updating costs relating to cardiovascular events also has a large effect. Because we now use higher estimates of cost across most categories (substantially so in some cases), the value of statins in preventing events increases. For both men and women, the net effect of the updates is to increase incremental QALYs and decrease incremental costs, although this does not lead to large changes in estimated cost-effectiveness.

Appendix 7 provides full results for all five simulated strategies at varying levels of cardiovascular risks, as well as a range of deterministic and probabilistic sensitivity analyses.

TABLE 16 Independent and cumulative impact of general updates to CG181 model:[10] incremental costs and effects of high-intensity statins (atorvastatin 20 mg/day) compared with no treatment

Scenario	60-year-old men with a 10% 10-year CVD risk			60-year-old women with a 10% 10-year CVD risk		
	Incremental cost (£)	Incremental QALY	ICER (£)	Incremental cost (£)	Incremental QALY	ICER (£)
CG181[10] base case	1248	0.299	4177	1290	0.340	3795
1. Correct error in annual risk increase in CG181[10]	961	0.359	2674	1080	0.384	2811
2. Scenario 1 and 2021 statin costs	938	0.359	2610	1056	0.384	2748
3. Scenario 1 and 2017–19 lifetables	961	0.359	2681	1077	0.380	2838
4. Scenario 1 and remove non-cardiovascular death benefit	925	0.289	3198	1050	0.324	3245
5. Scenario 1 and remove type 2 diabetes adverse event costs	950	0.359	2644	1069	0.384	2783
6. Scenarios 1–5 (all routine updates and corrections)	893	0.290	3079	1014	0.320	3172
7. Scenario 6 and new baseline utility model using HSE data	893	0.314	2841	1014	0.333	3048
8. Scenario 6 and new CVD event HSUVs from review	893	0.288	3101	1014	0.313	3239
9. Scenarios 6–8 (new utilities)	893	0.312	2863	1014	0.326	3113
10. Scenario 6 and new CVD event costs from review	385	0.290	1329	364	0.320	1138
11. Scenario 10 and apply costs for all deaths	426	0.290	1468	403	0.320	1262
12. Scenarios 6–8, 10 and 11 (new utilities and costs)	426	0.312	1365	403	0.326	1238
13. Scenario 6 and new model for first cardiovascular event	816	0.278	2935	823	0.321	2560
14. Scenarios 6–8, 10, 11 and 13 (all new data)	431	0.299	1441	409	0.333	1228

HSUV, health-state utility value; ICER, incremental cost-effectiveness ratio.

Accounting for competing risk

Before examining the impact that introducing adjustment for competing risks has on the cost-effectiveness of statins, it is useful to understand how it affects the modelled natural history of people at risk of CVD without accounting for any treatment effect. *Appendix 8*, *Figure 47*, provides model state occupancy graphs in two untreated cohorts with and without adjustment for competing risk of non-cardiovascular mortality. From these examples (see *Appendix 8*, *Figure 47*), we can see that the impact of adjusting for competing risk depends on a person's cardiovascular risk compared with an average person of their sex and age:

- A 60-year-old woman with a 10-year QRISK3-predicted risk of 10% has above-average risk. In *Figure 19*, we can see that people in this category have slightly shorter non-cardiovascular life expectancy than people of the same age and sex in the general population. Consequently, when we include this adjustment in the cost-effectiveness model, the cohort experiences somewhat diminished life expectancy. The unadjusted lifetables tell us that a woman of this age has around a 35% chance of surviving until her 90th birthday. However, once we adjust for the raised risk of non-cardiovascular death that is associated with a 10-year cardiovascular risk of 10%, that figure drops to

around 25%. A direct corollary of this is that the average woman with these characteristics will spend somewhat less time at risk of cardiovascular events, and we can see that the areas reflecting fatal and non-fatal cardiovascular history in the state occupancy graph (see *Appendix 8*, *Figure 47*) shrink between the unadjusted and adjusted versions.

- Conversely, a 60-year-old man with a 10-year QRISK3-predicted risk of 10% has below-average risk (note that in *Figure 19* empirical and modelled data show a slightly longer non-cardiovascular life expectancy than would be expected for an average person of that age and sex). Now we have the opposite result, that is the man spends longer alive in the model than the unadjusted lifetable would suggest. The man's chance of reaching 90 years of age rises from around 28% to around 38%. In addition, the man spends longer at risk of cardiovascular events and so the relevant areas grow instead of shrinking.

When we layer treatments effects, costs and QALYs on these dynamics, we derive cost-effectiveness results with similar characteristics (*Table 17*). When estimating the cost-effectiveness of statins, the impact of adjusting for competing risk depends on the cohort's cardiovascular risk compared with an average person of their sex and age:

- For the 60-year-old women with a 10-year QRISK3-predicted risk of 10%, expected QALYs in both intervention and control arms decrease by around 0.65, reflecting the cohort's below-average health. This means that a proportion of the cohort will die before they accrue all of the benefits of statins previously predicted for them. Consequently, health gains associated with high-intensity therapy (i.e. atorvastatin 20 mg/day), compared with no treatment, reduce by around 0.04 QALYs compared with the unadjusted model.
- Our 60-year-old men with a 10-year QRISK3-predicted risk of 10% were more healthy than their average contemporaries and so our cohort accrues around 0.6 QALYs per person more in both arms when adjusting for competing risk. This additional life expectancy potentially increases each man's capacity to benefit from statins. Therefore, we see the incremental benefits of high-intensity therapy (i.e. atorvastatin 20 mg/day), compared with no treatment, rise by a little under 0.04 QALYs per person compared with the unadjusted model.

TABLE 17 Effect of adjusting for competing risk of non-cardiovascular death on estimated cost-effectiveness of statins: 60-year-olds with a 10-year cardiovascular risk of 10%

	Absolute		Incremental			
Strategy	**Cost (£)**	**Effect (QALY)**	**Cost (£)**	**Effect (QALY)**	**ICER (£/QALY)**	**NHB at £20,000/QALY**
60-year-old men with a 10-year cardiovascular risk of 10%						
Unadjusted updated model						
No statins	6343	12.805				12.488
High-intensity statins	6774	13.104	431	0.299	1441	12.766
Adjusting for competing risk						
No statins	6943	13.460				13.113
High-intensity statins	7353	13.797	410	0.337	1217	13.429
60-year-old women with a 10-year cardiovascular risk of 10%						
Unadjusted updated model						
No statins	6567	12.730				12.402
High-intensity statins	6976	13.063	409	0.333	1228	12.714
Adjusting for competing risk						
No statins	6013	12.057				11.112
High-intensity statins	6443	12.350	430	0.292	1469	11.365

ICER, incremental cost-effectiveness ratio; NHB, net health benefit.

However, these adjustments affect treatment and non-treatment arms to a fairly similar degree. As a result, the cost-effectiveness of statins is not materially changed. The incremental cost-effectiveness ratio (ICER) for 60-year-old men with a 10-year QRISK3-predicted risk of 10% goes down by around £500 per QALY. For women with the same age and risk, the ICER goes up by a similar amount. In all cases, ICERs remain far below conventional thresholds representing an effective use of NHS resources.

Appendix 8, *Figure 54*, illustrates the same comparisons when analysed probabilistically. The same features are evident as in the deterministic results. For 60-year-olds with a 10% 10-year cardiovascular risk, adjusting for competing risk of non-cardiovascular death increases QALYs for men and decreases QALYs for women, although resulting cost-effectiveness estimates are not materially altered.

In *Appendix 8*, *Figure 48*, we depict the cost-effectiveness of statins for people of different ages and cardiovascular risks, and how adjusting for competing risk of non-cardiovascular death affects these results. Even before adopting this adjustment, the model suggests that statins represent a good use of resources for almost everyone. It is only for people aged ≥ 60 years with the lowest cardiovascular risk that statins represent poor value for money. However, adjusting for competing risk of non-cardiovascular death removes even this small subgroup. In practice, the distinction is moot if QRISK3 is used to predict cardiovascular risk, as it is essentially impossible for people in those age brackets to have 10-year risks low enough to enter the cost-ineffective zone. If such people did exist, then they would have extraordinary life expectancy, which is why the adjusted model concludes that it would still be good value to offer them statins, as there is every chance that even the oldest people would live to realise their benefit.

Appendix 8 provides full results from the updated model, adjusted for competing risk for all five simulated strategies at varying levels of cardiovascular risks, as well as a range of deterministic and probabilistic sensitivity analyses.

Incorporating direct treatment disutility

Introducing DTD to the analysis has a substantial impact on the results. *Table 18* shows cost-effectiveness results for 60-year-old men and women under our four DTD scenarios. For the permanent

TABLE 18 Effect of incorporating DTD on the estimated cost-effectiveness of statins

Strategy	Absolute		Incremental			NHB at £20,000/QALY
	Cost (£)	Effect (QALY)	Cost (£)	Effect (QALY)	ICER (£/QALY)	
60-year-old men with a 10-year cardiovascular risk of 10%						
No DTD						
No statins	6943	13.460				13.113
High-intensity statins	7353	13.797	410	0.337	1217	13.429
Permanent DTD						
No statins	6943	13.460				13.113
High-intensity statins	7353	13.370	410	−0.090	Dominated	13.002
Time-limited DTD						
No statins	6943	13.460				13.113
High-intensity statins	7353	13.558	410	0.098	4183	13.190
Diminishing DTD						
No statins	6943	13.460				13.113
High-intensity statins	7353	13.655	410	0.196	2097	13.288

TABLE 18 Effect of incorporating DTD on the estimated cost-effectiveness of statins (*continued*)

Strategy	Absolute		Incremental			NHB at £20,000/QALY
	Cost (£)	Effect (QALY)	Cost (£)	Effect (QALY)	ICER (£/QALY)	
60-year-old women with a 10-year cardiovascular risk of 10%						
No DTD						
No statins	6013	12.057				11.757
High-intensity statins	6443	12.350	430	0.292	1469	12.028
Permanent DTD						
No statins	6013	12.057				11.757
High-intensity statins	6443	11.963	430	−0.094	Dominated	11.641
Time-limited DTD						
No statins	6013	12.057				11.757
High-intensity statins	6443	12.125	430	0.068	6323	11.803
Diminishing DTD						
No statins	6013	12.057				11.757
High-intensity statins	6443	12.216	430	0.159	2708	11.894

NHB, net health benefit.

Note
All analyses include general model updates and adjustment for non-cardiovascular competing risk.

scenario (with a utility multiplier of 0.966), DTD throughout the period people are taking statins for primary prevention is enough to render the statins net harmful. Although the intervention provides around 0.3 QALYs, the small day-to-day disutility of taking the tablets amounts to more than 0.4 discounted QALYs over a lifetime, and so the tablets end up doing more harm than good. Assuming that DTD lasts for no more than 10 years (with either constant or diminishing detriment over that period) attenuates but does not eradicate the benefits of statins in these cohorts, and so the statins remain reasonable value for money, assuming that QALYs are valued at conventional levels.

We see the effect of differing DTD assumptions on the cost-effectiveness of statins across a range of ages and baseline cardiovascular event risks in *Appendix 8*, *Figure 50*.

Even though a lifetime's unremitting DTD represents a substantial decrement to expected quality of life, statins remain an effective use of resources for younger people with higher levels of risk. This is not only because people with high levels of risk stand to gain more from taking preventative statins (as they are more likely to have an event to prevent), but also because they spend less long in the primary prevention state (as they move to the event states more swiftly and they are also, now we adjust for competing risk of non-cardiovascular mortality, more likely to die of other causes). In contrast, people with lower levels of risk may need to take statins for a long time before realising benefits, and this becomes a poor trade-off when DTD is permanent. Older people, too, experience net harm from statins if they cannot get used to taking them, and this is because the lower life expectancy of older people gives them limited time in which to experience potential benefits of the intervention, while its harms are unavoidable.

For time-limited (10-year) DTD, the age–risk threshold at which statins become cost-effective is very close to the mean QRISK3-predicted risk observed in the population. Under this scenario, anyone with above-average risk stands to gain from treatment, whereas the model suggests that anyone with below-average risk will experience net harm.

If we can assume that DTD declines over time, then statins remain good value for everyone except people with a theoretically possible – although practically unlikely – profile reflecting extraordinarily good health for their age.

We show probabilistic versions of these calculations for a representative range of age–risk profiles in *Appendix 8*, *Figure 58*. In *Appendix 8*, *Figure 58*, the 'clouds' converge as age and risk rises, showing that DTD has less of an absolute effect on model outputs (owing to shorter time on preventative treatment with lesser life expectancy and higher event rates). However, net value for money remains relatively unaffected. In the cost-effectiveness acceptability curves, statins are always associated with less than 20% chance of cost-effectiveness when we assume permanent DTD (assuming we value QALYs at ≥ £20,000). Conversely, without DTD, statins are certain to be cost-effective as long as we value QALYs at ≥ £6000. The temporary DTD scenarios also result in a high probability of cost-effectiveness, with the exception of 10-year DTD in 80-year-olds with a 30% risk of cardiovascular event. Under this scenario, there is around a 50 : 50 chance that statins are worth paying for, and this is fairly invariant to the value we place on QALYs.

The interaction between life expectancy, level of risk and duration of DTD discussed above begins to suggest another way of conceptualising benefit–harm trade-offs. We have previously argued that the 'pay-off time', that is the minimum time until people can expect net benefit from a course of action with up-front harms and long-term benefits, may provide a useful heuristic for thinking about these issues in shared decision-making.[41] *Appendix 8*, *Figure 59*, shows cumulative incremental QALYs over time for four example profiles across our four DTD scenarios (we do not discount outcomes in this instance, as we take the view that it would be impossible for a patient to arrive at their own conception of the interaction between benefit and time while mentally adjusting for the fact that an interaction of that type is hardwired into the calculation).

Under the permanent DTD scenario, for a 50-year-old with a 10-year CVD risk of 5%, a decision to take statins would confer net QALY gains only after 48 years of treatment. For 60-year-olds at 10% risk, 70-year-olds at 20% risk and 80-year-olds at 30% risk, the expected pay-off times are 36 years, 25 years and 22 years, respectively. When we assume temporary DTD of one form or another, the expected pay-off times are typically in the range of 10–20 years.

Interaction of competing risk and direct treatment disutility

Bringing the analyses above together, we can look at the combined effect of competing risk of non-cardiovascular death and DTD on the effectiveness and cost-effectiveness of statins for the primary prevention of CVD.

To do this, we present a 4 × 4 cross-categorisation of scenarios, within each of which we derive results for people at different ages and different levels of baseline risk. For competing risk calculations, we present two additional scenarios in which we halve and double the cohort's hazard of non-cardiovascular death. These scenarios are representative of a decision problem in which people are atypically healthy or atypically well to a degree over and above what we would expect by adjusting for their cardiovascular risk alone.

Figure 20a visualises the expected incremental QALY gains associated with high-intensity statins compared with none in each of these scenarios. Without DTD, statins are associated with very little disutility in the model and, therefore, statins generate some degree of QALY benefit for people at any age and any level of cardiovascular and competing risk (see first column *Figure 20a*). However, when we introduce DTD, the threshold at which treatment confers net QALY gains begins to depend on age. For someone who is persistently averse to pill-taking (implying lifelong DTD; see last column of *Figure 20a*), many combinations of age and risk result in statins doing more harm than good (see black area in *Figure 20a*). For example, people with such preferences in their mid-70s and older would need a 10-year QRISK3-predicted risk of over 30% before statins would be net beneficial. If people had additional

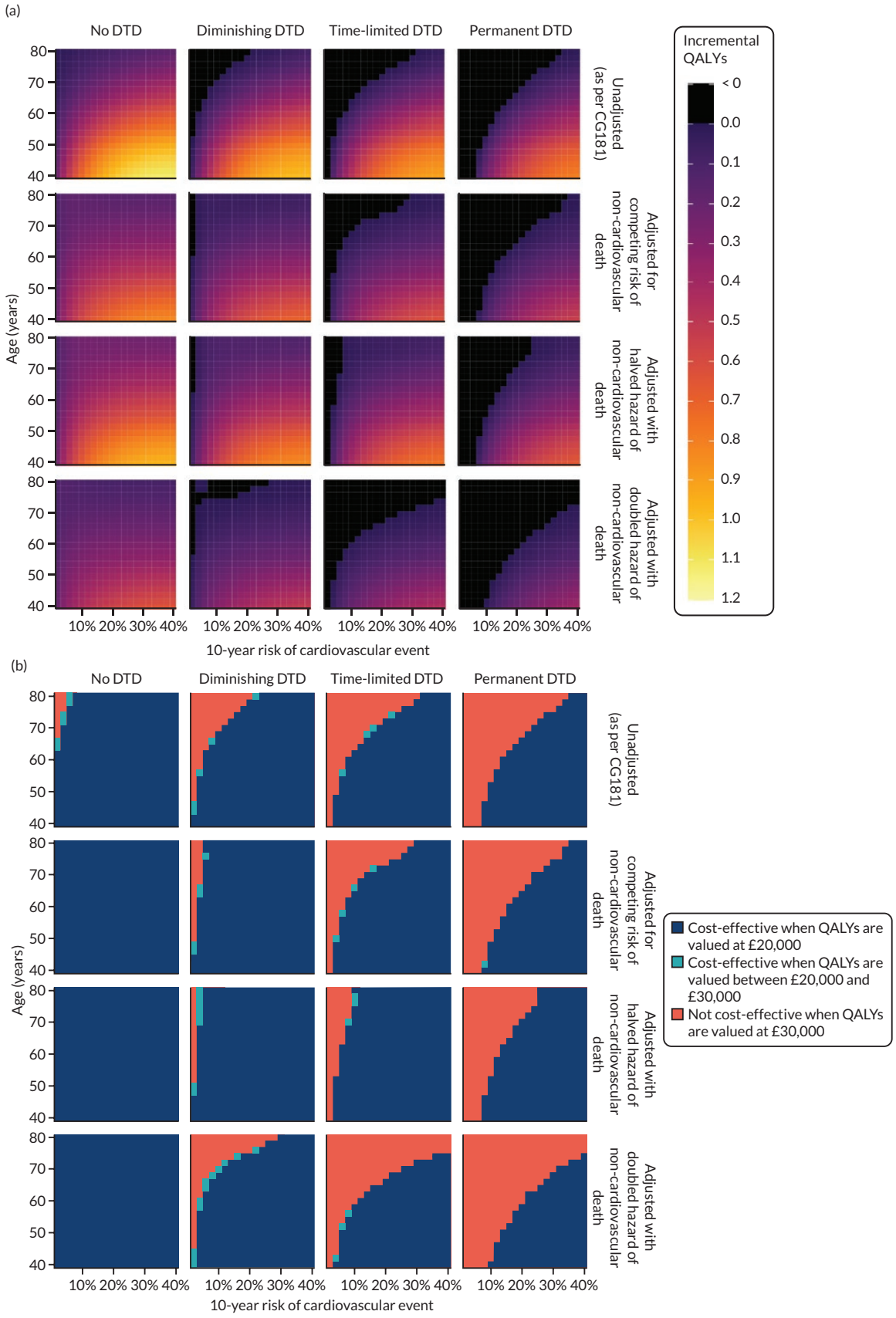


FIGURE 20 Clinical effectiveness and cost-effectiveness of high-intensity statins, as a function of age and cardiovascular risk, with different levels of DTD and competing risk of non-cardiovascular death. (a) Effectiveness (incremental QALYs); and (b) cost-effectiveness (when QALYs are valued at £20,000–30,000).

long-term conditions leading to a doubled risk of non-cardiovascular death, then that threshold would rise to 40%. Even if we assume taking pills is something people get used to (i.e. time-limited DTD), it is easy to find combinations of age and risk where statins' DTD outweighs their cardiovascular benefits.

Figure 20b provides a similar analysis but introduces expected costs to the equation to establish the circumstances in which statins would be judged to provide an effective use of NHS resources (when QALYs are valued at NICE-recommended levels of £20,000–30,000). The combinations of characteristics for which statins do not provide good value for money are similar to characteristics for which they generate QALY loss (except under unusual circumstances, a technology will not be cost-effective if it is not associated with QALY gains). However, there are a small number of combinations where, although the model predicts positive QALY gains for statins, the positive QALY gains are so small that the cost of the drugs outweighs the gains (e.g. under the permanent DTD scenario, 50-year-olds with a 10% risk of cardiovascular event and an adjusted but unaltered hazard of non-cardiovascular death, as such people expect a tiny lifetime benefit of 0.006 QALYs, but at a cost that equates to an ICER of around £44,000 per QALY).

As a scenario analysis, we also explored applying DTD as an absolute decrement rather than a relative multiplier, and this results in a slightly greater impact for DTD. For example, for 80-year-olds under time-limited and permanent DTD scenarios, statins do more harm than good at all levels of risk we analyse (see *Appendix 8*, *Figure 60*).

Discussion

Main findings

When it comes to state-transition decision models, the question is not whether or not to account for competing risks, but how to do so. Our analysis shows that, where competing risks are handled in a naive manner (e.g. assuming population lifetables for all-cause death), analyses overestimate the clinical effectiveness and cost-effectiveness of preventative interventions in people with above-average risk and underestimate the clinical effectiveness and cost-effectiveness in people with below-average risk. In the case of statins for the primary prevention of CVD, the intervention appears to be almost universally cost-effective in a way that renders these biases of limited impact. However, we have shown that the potential for meaningful differences exists. Indeed, one only has to imagine high-intensity statins cost £18 per pack instead of £1.10, and appropriate adjustment for competing risk of non-cardiovascular death would make the difference between the intervention meeting and not meeting conventional thresholds of cost-effectiveness for some people, for example 75-year-old men with a 10-year cardiovascular risk of 15% (unadjusted ICER compared with no treatment, £25,700/QALY; adjusted ICER, £18,100/QALY).

Incorporating DTD has a more immediately obvious effect on the cost-effectiveness outputs of the model. However, although we see no reason for decision models not to include the most robust estimates of competing risks possible in their base cases, we would hesitate to recommend that modellers should include population-average DTD in their base-case cost–utility results, as this would result in statins being recommended for only people who appear in the dark blue areas in the bottom-right of *Figure 20b* for whichever DTD scenario decision-makers prefer. In *Chapter 5*, we argued that, rather than assuming blanket disutility, we should provide decision-makers with evidence of circumstances under which, and people for whom, DTD might tip the balance of benefits and harms (if any). In turn, decision-makers should use this information to provide guidance to prescribers that can inform shared decision-making. This case study illustrates the point well.

To return to our example of a 75-year-old man with a 10-year cardiovascular risk of 15%, without accounting for DTD, we would expect the man to achieve net QALY gains from statins (i.e. an expected value of 0.19 QALYs, which is equivalent to over 2 months in perfect health). However, once we

introduce DTD, that expectation reduces. Under the diminishing DTD scenario, the man can expect fewer than 0.06 QALYs, whereas the time-limited and permanent DTD scenarios predict net QALY loss.

Nevertheless, even if we think the permanent DTD scenario is the best way to capture population-level average disutility, we would not argue in favour of adjusting everyone's expectation to account for it (which would have the effect of rendering statins poor value for money in people with these characteristics). This is because – as clearly shown in *Chapter 5* – some people anticipate negligible disutility from taking statins and, indeed, some people may even anticipate benefit over and above the directly clinical effects (i.e. 'peace of mind'). To deny such people access to an effective treatment would clearly not maximise societal welfare, even if the average person would not feel the same. Therefore, we suggest that the appropriate way to make use of this information is as an objective basis on which decision-makers can identify what NICE refers to as 'preference-sensitive decision-points'.[125] In this paradigm, guidelines should help prescribers to summarise benefits and harms of possible options for people for whom they are indicated, and this should include the process characteristics underlying DTD.

Precisely how such information makes it into shared decision-making is an unanswered question. It is theoretically possible to envisage ex ante preference elicitation, along similar lines as our experiment, which could be integrated into a personalised QALY-maximising analysis to provide recommendations for individual patients, and, unquestionably, this would be practically onerous, but, arguably, it would be unnecessarily prescriptive. However, we think it is useful to augment prescribers' understanding of the strength of preference for avoiding a technology that would be necessary to outweigh its expected benefits, and our findings give an example of how this might be possible.

Since CG181, there have been two CEAs[143,144] of statins for the primary prevention of CVD that predicted cardiovascular events and non-cardiovascular death based on a common set of risk factors. To do this, the analyses used either separate models[144] or cause-specific survival models.[143] Like our relative survival model, these approaches should accurately predict time spent living with CVD and, therefore, QALYs because they capture the crucial correlation between cardiovascular risk and competing risk of non-cardiovascular death. However, neither analysis tested whether or not its results were sensitive to this competing risk adjustment, that is neither analysis modelled scenarios where risk of non-cardiovascular death was assumed to be independent of cardiovascular risk factors for comparison. In addition, one of these analyses found that cost-effectiveness was sensitive to DTD in the form of an additive decrement ascribed to 'pill burden', which was applied to each QALY.[144] Another primary prevention model[124] has also reported that the cost-effectiveness of statins is sensitive to an arbitrary disutility for DTD.

There is recent, compelling evidence that many self-reported muscle symptoms in people taking statins can be explained as 'nocebo' effects.[43] Although this finding may represent a fascinating psychological insight, it is of limited practical value to prescribers, as few people experiencing pain when taking a statin will easily accept that their symptoms are 'all in the mind'. However, we argue that DTD provides a helpful way to conceptualise and quantify the authentic and predictable harm that such people experience. Authors usually cite process and inconvenience factors to explain why people ascribe disutility to taking a preventative medicine they have been assured is benign.[40] However, it is also likely that part of the internal calculus reflects (1) a degree of mistrust that the substance truly has no adverse effects and (2) a reluctance to become 'a patient' who – among other inconveniences – will henceforth be on-guard for unpleasant symptoms.[145] Although few people would describe it in such terms, no one wants to volunteer for a nocebo effect. Therefore, by quantifying the things that people ex ante want to avoid from preventative treatment, we believe that we capture some or all of the subtler harms that people taking them report ex post. As explored in this chapter, this enables us to balance these harms against the expected benefits and costs of treatment to estimate whether or not we expect net benefit overall.

Limitations

First, we have not been able, as originally intended, to take account of the extent to which specific co-existing long-term conditions might complicate the issues explored in this chapter. In particular, we wanted to look at type 1 diabetes and CKD, as NICE identified these conditions as areas of interest in the surveillance proposal in which it announced its intention to update CG181.[13] However, we found that including additional binary covariates for one or both of these factors did not improve the fit of our relative survival models. Therefore, this implies that the impact of type 1 diabetes and CKD on cardiovascular risk is well captured by the QRISK3 algorithm, and the factors do not differentially confound the relationship between cardiovascular risk and non-cardiovascular mortality. We also found that type 1 diabetes and CKD had no meaningful effect on the type of first cardiovascular event people experience. Having found no clear point of differentiation, it would not have been meaningful to stratify our analyses. Of course, it would also be possible to tailor other model inputs (e.g. baseline utility, event disutility, cost of events) to represent people with particular long-term conditions, and this might affect outputs in non-trivial ways.

Second, our relative survival models use predicted cardiovascular risk (i.e. QRISK3 10-year predicted risk) as an overarching indicator of non-cardiovascular life expectancy. We believe that we achieved a very good fit to observed data in this way (see *Figure 19*). Nevertheless, it would be possible to construct a more sophisticated model that, instead of using a summary risk prediction measure, estimates relative survival as a function of each of the individual covariates on which the prediction itself relies. For example, an 80-year-old non-smoking man with type 2 diabetes and SBP of 140 mmHg has an identical 10-year QRISK3-predicted CVD risk to an 80-year-old moderate-smoking man with no diabetes and SBP of 166 mmHg. If the factors that distinguish these two individuals affect their non-cardiovascular life expectancy differentially, then our relative survival model will fail to capture this. By accounting for these factors, it might be possible to achieve an even more accurate prediction of life expectancy. However, as noted above, we found that including terms for type 1 diabetes and/or CKD did not improve the fit of our relative survival models. Nevertheless, we cannot rule out the possibility that other variables would explain some residual heterogeneity between observed and modelled survival expectation.

Third, because secondary prevention of CVD is beyond the scope of our project, we did not review any evidence about the natural and treated history of people who have had a cardiovascular event. For all secondary transitions, the model relies on the same inputs that the developers identified for CG181.[10] Although this part of the pathway is outside our decision problem, it has an important impact on our estimates of lifetime costs and effects, as it defines some of the value that an intervention provides by preventing first events. We suggest that any future updates to the model should review evidence in this area, even if secondary prevention is not the analysts' focus.

Fourth, we do not make any adjustments to the model's effectiveness inputs to account for imperfect patient adherence to statins, and this means we effectively assume adherence is identical to that observed in the intention-to-treat trials that underpin the effect estimates. If adherence in practice is worse than in trials, then the model is likely to overestimate, to some degree, the clinical effectiveness and cost-effectiveness of statins.

Finally, the model compares all-or-nothing strategies. In reality, the counterfactual to offering statins to a given cohort is not never offering them statins, it is not offering statins for the time being, with the option of revisiting the decision later. To simulate this decision problem, we would require detailed longitudinal data with which to project the development of risk factors over time. It would also probably necessitate moving away from a cohort model to a stochastically evaluated individual patient simulation. However, we would argue that this analysis highlights some of the major advantages of analytically evaluated cohort models. The kind of many-way scenario analyses we have been able to generate would be computationally intractable and muddied by Monte Carlo error in a patient-level simulation, and we feel sure that the kind of analytical flexibility from which our analysis benefits outweighs the flexibility in representing the pathway that would come with a patient-level simulation.

Conclusion

This analysis has shown that updating the CG181 model with newer model inputs did not materially change the conclusion that statins are an effective use of healthcare resources. In the case of statins for the primary prevention of CVD, the intervention appeared to be almost universally cost-effective in a way that renders the impact of including competing risk inconsequential. However, we argue that failure to account for competing risk in CEAs of primary prevention strategies will produce biased results and the impact of this omission is likely to become more apparent for interventions with relatively higher costs compared with their health benefits. Incorporating DTD had a more immediately obvious effect on the cost-effectiveness of statins. We advise that the impact of including DTD in sensitivity analyses on the outputs of a decision-analytic model should be an integral component of CEAs of primary prevention strategies.

Chapter 7 Cost-effectiveness analysis accounting for competing risks and direct treatment disutility: bisphosphonates for the primary prevention of osteoporotic fragility fracture

Background

Selection of the case study

The decision to offer oral bisphosphonates for the primary prevention of osteoporotic fragility fracture is a second potentially illuminating case study for examining the impact of competing risks and DTD on CEAs. The risk factors for fragility fracture include many behavioural (e.g. smoking) and pathological (e.g. type 1 diabetes) factors that are also associated with shorter life expectancy. Failing to account for these factors could lead to inflated estimates of the value of medicines that reduce the risk of fracture. Furthermore, although there is little doubt that oral bisphosphonates are effective in reducing incidence of fragility fracture, bisphosphonates are inconvenient to take, and this raises the possibility that DTD may attenuate or even outweigh the gains that previous CEAs have estimated.

NICE initially recommended two oral bisphosphonates (i.e. alendronic acid and risedronate sodium) in in its Technology Appraisal 160 in 2008.[146] A subsequent appraisal (i.e. TA464[12]) confirmed this decision and added a third oral medicine in the class (i.e. ibandronic acid) to the recommended options. The evidence available to the decision-making committee for TA464[12] included a CEA, synthesising evidence on the benefits, harms and costs of preventative treatments, including oral bisphosphonates. The analysis concluded that oral bisphosphonates are likely to represent an effective use of NHS resources for anyone whose 10-year risk of MOF exceeds 1.5%.[147]

The same authors updated their model as part of a further health technology assessment (HTA) for a subsequent NICE appraisal, and this focused on antiosteoporosis medicines other than bisphosphonates, but included bisphosphonates as comparators, although NICE subsequently chose to suspend the appraisal.[148] The updated model found that a somewhat higher level of risk, than in TA464,[12] would be necessary for oral bisphosphonates to provide reasonable value for money, although the precise threshold is not quantified.[149]

The model underpinning these analyses was a discrete-event simulation. Unlike the cohort model explored in *Chapter 6*, discrete-event simulations work by generating a virtual population of people and simulating their lives one by one. Discrete-event simulations handle competing events by randomly generating next-event times for all outcomes of interest, processing the event that will occur first and then, depending on event type and model structure, moving on to the next event or recalculating some or all next-event times to reflect the simulated person's updated history. The simulation may also terminate (e.g. if the event is death).

Given adequate data and implementation, discrete-event simulation is an appropriate way of accounting for competing events and, because the model handles them simultaneously, it is appropriate to parameterise each event distribution using time-to-event methods that censor for competing events. This is because, in a patient-level simulation as in clinical reality, events compete naturally, and the occurrence of some events will preclude the occurrence of others. In the case in hand, some simulated

people will experience hip fracture before death; however, some people will experience death first, thereby precluding a fracture event (although the model 'knows' when that person was destined to experience a fracture had death not intervened).

Therefore, in contrast to the situation where we want to estimate the probability that a single event in isolation will occur (as in the epidemiological analyses in *Chapters 2* and *3*), modellers developing simulations with multiple events need inputs for each that censor for intervening events. In the case in hand, we actively want our estimates of time to hip fracture to reflect a world in which death is not possible (e.g. relying on a Kaplan–Meier estimator censoring for death), as the model will simultaneously and independently apply an estimate of time to death. So long as both inputs represent valid estimates for the modelled population, the incidence of hip fracture observed in the model will replicate the Aalen–Johansen estimator in a real population.

However, as with a cohort model, if the estimate for any one of our competing events is biased, then we will have biased results for all outcomes. Again, a commonly overlooked question is whether or not unadjusted general population lifetables represent an appropriate estimate of life expectancy for the people the model simulates. In a patient-level model, we have information about some characteristics for each person simulated. It is common to use the age and sex of the simuland to inform the distribution from which the model draws the time to all-cause death. However, other characteristics may also be associated with greater or lesser life expectancy. In the case in hand, we are particularly interested in predicted fracture risk. If people with high fracture risk also have an increased risk of other-cause death and we fail to account for this, then we will overestimate the number of fractures that occur and this, in turn, will overstate the clinical effectiveness and cost-effectiveness of any intervention that has the potential to reduce fracture incidence.

Previous models have estimated that the benefits of bisphosphonates for the average person are, in absolute terms, small. TA464[12] found that, when compared with no treatment, alendronate is associated with an average health gain no greater than 0.00247 QALYs, even in the highest-risk tenth of people.[12] The 2020 HTA[149] introduced a little more benefit for oral bisphosphonates, but alendronate still conferred only mean gains in the range of 0.0001–0.0058 QALYs (equivalent to up to 2 quality-adjusted days of life in perfect health), depending on baseline risk.

These small benefits should not be casually dismissed, given the low cost of the intervention and the large population who could expect, on average, to gain. Nevertheless, it is clear that it would not take much to offset the expected gains. Both TA464[12] and the 2020 HTA[149] incorporate an estimate of QALY loss owing to adverse gastrointestinal effects for a proportion of people taking oral alendronate. However, these analyses do not reflect the fact that, even when well tolerated, oral bisphosphonates are inconvenient to take. As we have seen (see *Chapter 5*), even when taken weekly, oral bisphosphonates are associated with non-trivial DTD (significantly greater than for daily statins). Therefore, it is plausible that the routine downsides of taking bisphosphonates might attenuate or outweigh their benefits in preventing fractures, although this trade-off has not previously been explored.

Our aim was to explore the impact that better accounting for competing risk of death and incorporation of DTD might have on the estimated cost-effectiveness of bisphosphonates. TA464[12] stipulates that prescribers should offer bisphosphonate treatment 'when [it] is appropriate, taking into account [the person's] risk of fracture, their risk of adverse effects from bisphosphonates, and their clinical circumstances and preferences' (© NICE 2017 Bisphosphonates for Treating Osteoporosis. Available from www.nice.org.uk/guidance/ta464. All rights reserved. Subject to Notice of rights). Although fracture risk and adverse events are central to previous analyses of the cost-effectiveness of bisphosphonates, there has been little formal consideration of how decision-making might be affected by people's clinical circumstances and preferences. The methods introduced in this project enable us to explore these dimensions and weigh them against the benefits and harms that existing models estimate.

Methods

The CEA reported here adopts and adapts the model developed for TA464 to address the decision problem (*Table 19*). Full details of the modelling approach can be found in Davis *et al.*[149,150] We did not make any modifications to this model, with the exception of how the model implements the impact of persistence (see below).

Model overview

The model is a patient-level discrete-event simulation. *Figure 21* illustrates the structure of the model and *Table 19* summarises key design criteria. Where state-transition models define a healthcare pathway in terms of states, discrete-event models proceed by way of events. The events that are possible in the TA464 model[12] are fractures (divided into four categories of hip, vertebral, proximal humerus and wrist), admission to full-time care and death (fracture related and other cause). Simulated people who experience fractures incur costs and disutility, and their risk of additional negative events (e.g. further fractures, admission to full-time care, death) increases.

Our study focused exclusively on the pairwise comparison between oral alendronate and no treatment. Our DTD elicitation exercise did not distinguish between different oral bisphosphonates, and alendronate is, by some distance, the most commonly prescribed chemical in the class, consistently accounting for over 80% of prescriptions of agents classified in *British National Formulary* section 6.6 (drugs affecting bone metabolism).[151]

TABLE 19 Decision-analytic model for bisphosphonates for primary prevention of osteoporotic fragility fracture – key design criteria

Decision-analytic model	Criterion
Decision problem	To assess the cost-effectiveness of oral alendronate compared with no treatment at varying levels of absolute fracture risk, as defined by the QFracture-2012 risk assessment tool
Intervention	Oral alendronate
Comparators	No treatment
Model type	Patient-level discrete-event simulation
Population	People (men and women) eligible for risk assessment under NICE CG14688
Setting	Primary care services in NHS England
Time horizon	Lifetime
Study perspective	NHS and Personal Social Services in England
Costs	• Acquisition of bisphosphonates and associated monitoring • Treating subsequent osteoporotic fracture-related events • No costs assumed for establishing baseline risk of fracture (e.g. administering and calculating QFracture-2012)
	Measured using GBP (£) at 2019–20 prices
Consequences	Impact on health status
	DTD
	Measured using QALYs
Discounting	3.5% for costs and consequences
Cost-effectiveness threshold	NICE-recommended threshold of £20,000 per QALY gained

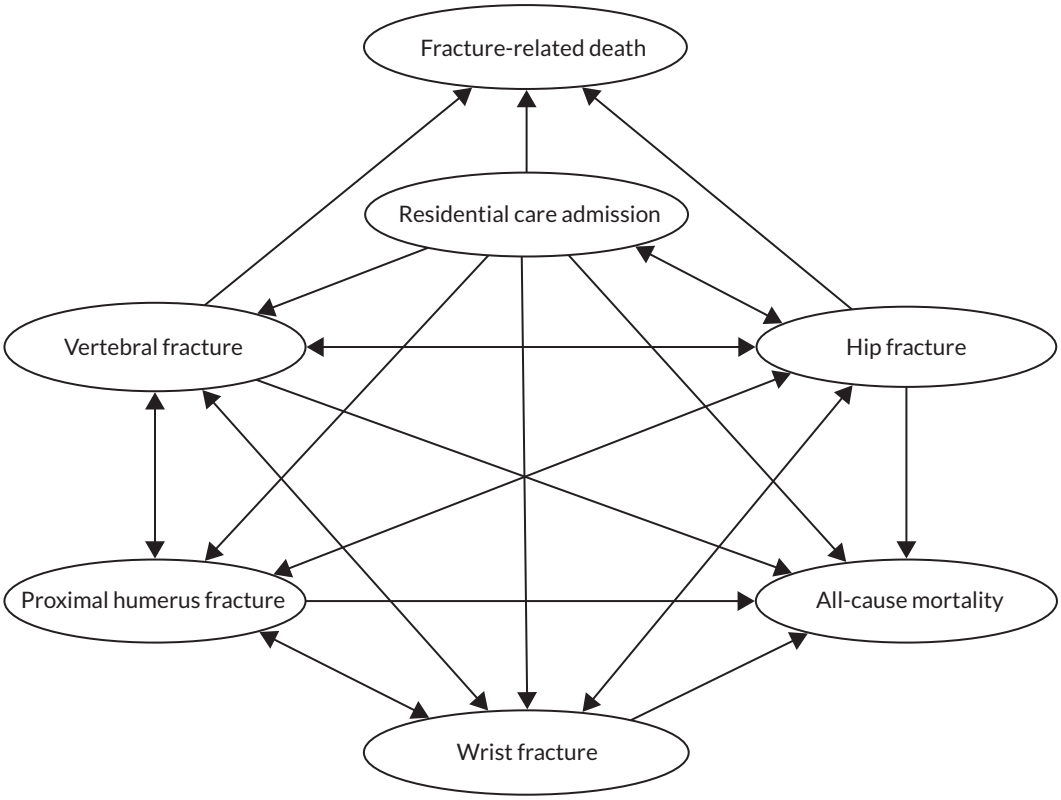


FIGURE 21 Structure of discrete-event model: events that can occur in a simulated person's lifetime.

General model updates

We performed fewer general updates to the bisphosphonates model than we did for the statins analysis. Producing a revised best estimate of the cost-effectiveness of bisphosphonates is beyond the scope of this project and analysis, therefore, focuses on exploring whether or not accounting for competing risks and DTD would have materially affected the historical analyses. One exception is that we have updated how the model implements persistence with oral therapy (see below), as this not only influences the effectiveness of bisphosphonates but also has potentially important implications for DTD, which is one of our central concerns.

The 2020 bisphosphonates HTA[149] introduced some other modifications to the TA464 model[12] that we have adopted as detailed below.

Duration of bisphosphonate therapy

The TA464 model[147] assumed that all people take oral bisphosphonates for 184 days, as this is the mean duration of treatment persistence found in a systematic review of observational cohort studies.[152] The 2020 HTA[149] updated the assumed duration of treatment to 1.6 years for alendronate, using data from an analysis of UK primary care data.[153] In neither case did the models account for patient-level variation in persistence, rather the models simulated 100% of patients persisting with treatment for the fixed period specified, on the assumption that costs and benefits are linearly related to duration of treatment.

In our update of the model, we have relaxed this assumption and have incorporated an estimate of patient-level variability. We used more recent UK primary care data on persistence to osteoporosis medicines.[154] To reflect the primary prevention decision problem, we used data from people who were treatment naive. Using digitising software (Engauge 12.1), we extracted data from the Kaplan–Meier graph depicting discontinuation from oral bisphosphonates and reconstructed synthetic patient-level data using the algorithm of Guyot *et al.*[155] To check the accuracy of this process, we generated a

Kaplan–Meier graph from the synthetic data and overlaid it on the published curve, finding an extremely close fit. To define a sampling distribution for time to discontinuation, we fitted various parametric models to the synthetic data set, and found that we could best describe the data using a log-normal distribution with a mean of 2.50 (95% CI 2.48 to 2.52) and a standard deviation of 1.74 (95% CI 1.72 to 1.75). This equates to a restricted mean treatment duration of 22.1 months (assuming no one is treated beyond the nominal maximum of 5 years). In the updated model, each simulated patient receives a random variate drawn from this distribution (capped at 5 years) as their duration of therapy with alendronate.

Health-related quality of life

As in TA464, the model estimates quality of life in the absence of fractures, using a published regression on HSE data.[156] For multipliers reflecting lost utility in the year of a fracture event and subsequently, we adopted the updated values used in the 2020 HTA,[149] which mostly originate from the International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS).[157–161]

Resource use and costs

The model assumes an NHS and Personal Social Services perspective (price year 2019–20).

We updated key unit costs to present-day estimates:

- Dual-energy X-ray absorptiometry (DEXA) scan: £76.62 (average weighted according to activity of all codes from *NHS Reference Costs* 2019–20).[162]
- GP appointment: £39.[163]
- Alendronate pack: £0.87.[139]

We also followed the updates from TA464 costings that the 2020 HTA[149] introduced:

- Accounting for monitoring costs for people on alendronate (i.e. one GP appointment per year and one DEXA scan per 5 years, annualised as 0.2 per year).
- Estimating full-time care costs using a 50 : 50 split of residential : nursing care. When privately met contributions (36%) are deducted, this amounted to an annual cost of £23,562 in 2013–4, which we inflated, as below.

For all other costs (e.g. acute and ongoing care following fracture events, home help, residential care), we uplifted the unit costs used in TA464 to 2019–20 levels using standard inflators.[163]

Treatment effectiveness

We took our estimates of the effectiveness of alendronate in preventing four categories of fragility fracture from TA464. (Note that these estimates are the outputs of the authors' corrected network meta-analysis, see corrigendum to Davis *et al.*[147])

Adverse drug events

TA464 accounts for a proportion of people taking alendronate experiencing upper gastrointestinal symptoms, and we have retained this feature unchanged.

New model features specific to this project

Accounting for competing risk of non-fracture death

To estimate non-fracture death in people at risk of osteoporotic fragility fracture, we used identical methods to those we adopted for non-cardiovascular death in people at risk of CVD (see *Chapter 6*, *Accounting for competing risk of non-cardiovascular death*).

First, we fitted a model to estimate average population fracture risk as a function of age and sex (see *Appendix 9*, *Table 57* and *Figure 61*). We noted that, in the CPRD data set, a relatively consistent exponential increase in risk throughout the first nine decades of life tails off somewhat in people in their nineties. We found it necessary to use a seventh-order polynomial term to capture this shape adequately. This feature is contrary to expectation, as there is no mathematical characteristic of the QFracture-2012 model that would lead to a waning of hazard.[26] Therefore, we think it is likely that selection effects in the underlying data set led to over-representation of nonagenarians with QFracture-2012 estimates that are low relative to expectation. To explore the impact of this issue, we fitted an alternative model on a restricted data set that comprised only people younger than 90 years, allowing the model to project the observed trend from people aged 30–89 years for people in their nineties, and in this case a quartic function sufficed (see *Appendix 9*, *Table 57* and *Figure 61*).

As for the non-cardiovascular death model in *Chapter 6*, we fitted a relative survival model to estimate the multiplicative difference in time to non-fracture death between a person in the CPRD extract and someone of the same age and sex in the general population. Again, our critical covariate is $\Delta\text{logit}(Q)$, that is the difference (on a log-odds scale) between each individual's predicted 10-year QFracture-2012 risk of major fracture and the average score for a person of the same age and sex, as estimated in the models described above.

We fitted a simple, univariable model with $\Delta\text{logit}(Q)$ as the only covariate and a more complex one with $\Delta\text{logit}(Q)$, age, polynomial terms for both and interactions between them, as per *Equation 1*. We tried models with $\Delta\text{logit}(Q)$ defined using each of the QFracture-2012 prediction models in *Appendix 9*, *Table 57*, and found that the relative survival model fitted better (with meaningfully lower AIC) when we used the model fitted on only people younger than 90 years. Therefore, this was the version of the relative survival model we took forward.

Table 20 shows outputs of the relative survival models for men and women.

Figure 22 shows estimates of non-fracture mortality generated in the way described above, compared with empirical data across different categories of cardiovascular risk and age. The empirical Kaplan–Meier curves represent observed non-fracture mortality (censored for fracture death) in the CPRD extract for people of the stated age, with baseline QFracture-2012 predictions in the specified brackets (see *Figure 22*). For our modelled estimates, we start from ONS 3-year lifetables for England and Wales (we use 2009–11 tables, as this is in the middle of the period covered by the CPRD data). We adjust the data to remove fracture deaths, estimated using proportions recorded under ICD-10 code M80 in the ONS's 'Deaths registered in England and Wales' series. For each combination of risk and age bracket, we calculate HRs, as described above (for comparability, we fit at the mean QFracture-2012 prediction and age observed within that category in the CPRD data), and apply the HRs to the ONS curves, and this produces the adjusted curves shown in *Figure 22*.

The fitted models provide a less strikingly accurate fit to the observed data than we saw with non-cardiovascular mortality, but still represent a substantial improvement over the unadjusted estimates. Larger coefficients are estimated for the polynomial terms in the more complex model, meaning that it diverges from the simple model to a somewhat greater extent than we saw for non-cardiovascular mortality.

Some instances in which the fitted models appear to depart from the empirical data seem to be due to incoherencies in the observed curves. For instance, it appears that women aged 60–69 years with a 10-year risk of less than 1% and women a decade older with a 1–2% risk have worse survival than the models predict. However, if this is true, then it means that women at this low risk have worse survival than women with higher fracture risk, which is both hard to explain and inconsistent with the patterns seen elsewhere in the data, where increasing risk is invariably associated with worse survival.

TABLE 20 Relative survival models: non-fracture mortality as a function of predicted fracture risk and age in men and women

Parameter	Simple model, HR (95% CI)	Polynomial model, HR (95% CI)
Men		
Δlogit(Q)	0.7216 (0.7163 to 0.7270)	1.7108 (1.6808 to 1.7409)
$\Delta\text{logit}(Q)^2$		−0.2025 (−0.2215 to −0.1835)
Age		7.69×10^{-3} (6.87×10^{-3} to 8.51×10^{-3})
Age^2		1.17×10^{-5} (-1.03×10^{-5} to 3.36×10^{-5})
Δlogit(Q) × age		−0.0218 (−0.0240 to −0.0195)
$\Delta\text{logit}(Q)^2 \times$ age		2.05×10^{-3} (6.65×10^{-4} to 3.44×10^{-3})
Δlogit(Q) × age^2		-1.66×10^{-4} (-2.13×10^{-4} to -1.19×10^{-4})
$\Delta\text{logit}(Q)^2 \times \text{age}^2$		2.93×10^{-5} (1.89×10^{-6} to 5.66×10^{-5})
AIC	5,252,183	5,239,595
Women		
Δlogit(Q)	0.8588 (0.8507 to 0.8668)	1.5458 (1.5081 to 1.5834)
$\Delta\text{logit}(Q)^2$		0.2280 (0.1987 to 0.2572)
Age		-3.07×10^{-3} (-3.97×10^{-3} to -2.16×10^{-3})
Age^2		2.19×10^{-4} (1.97×10^{-4} to 2.41×10^{-4})
Δlogit(Q) × age		-1.04×10^{-3} (-3.64×10^{-3} to 1.55×10^{-3})
$\Delta\text{logit}(Q)^2 \times$ age		−0.0163 (−0.0184 to −0.0142)
Δlogit(Q) × age^2		-5.30×10^{-4} (-5.79×10^{-4} to -4.80×10^{-4})
$\Delta\text{logit}(Q)^2 \times \text{age}^2$		2.07×10^{-4} (1.66×10^{-4} to 2.48×10^{-4})
AIC	5,172,844	5,164,693

We incorporated the relative survival models into the health economic decision model by calculating a fitted HR for each sampled patient and applying it when calculating their life expectancy.

Incorporating direct treatment disutility

We explored DTD using the same four scenarios as for the statins model: (1) no DTD, (2) 'permanent' DTD (i.e. full DTD applies over the entire period for which the simulated person is taking the bisphosphonate), (3) 'time-limited' DTD (i.e. full DTD while taking the drug up to a maximum 10 years) and (4) 'diminishing' DTD (i.e. linear decline from full to no DTD over 10 years, applied while taking the drug). The DTD multiplier for bisphosphonates from *Chapter 5* was 0.934.

Deriving results

For TA464, the modellers presented results from a single model run comprising 2 million virtual people (c. 200,000 per risk-stratified tenth), with parameter uncertainty propagated at the individual level (i.e. the model samples new parameter values from distributions reflecting uncertainty in their true value for each patient). Our preliminary investigation suggested that there is still non-trivial Monte Carlo error in the model with that many runs, but this generally appears to stabilise after around 4 million patients. Therefore, our base-case results summarise the outputs of 5 million people (c. 500,000 per tenth).

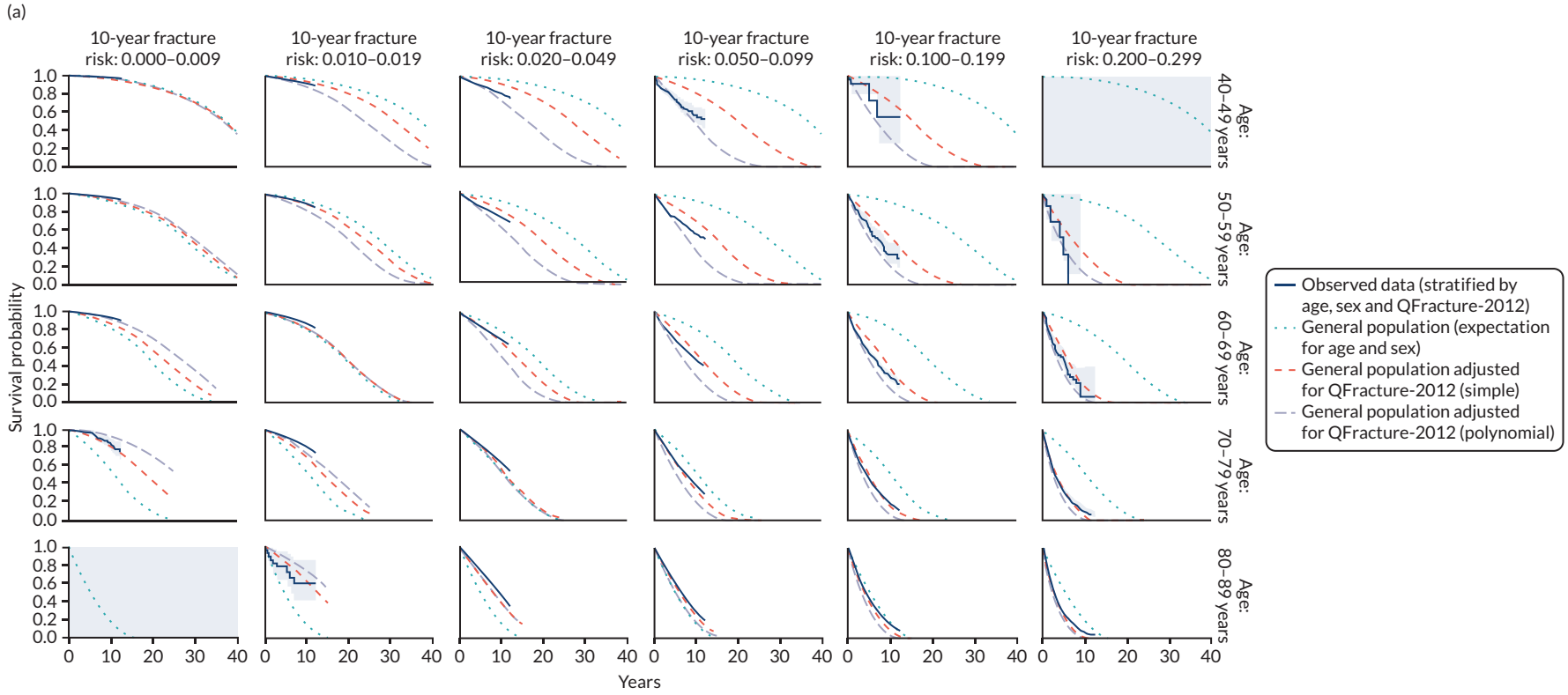


FIGURE 22 Fitted relative survival model for non-fracture mortality compared with empirical data. (a) Men; and (b) women. (*continued*)

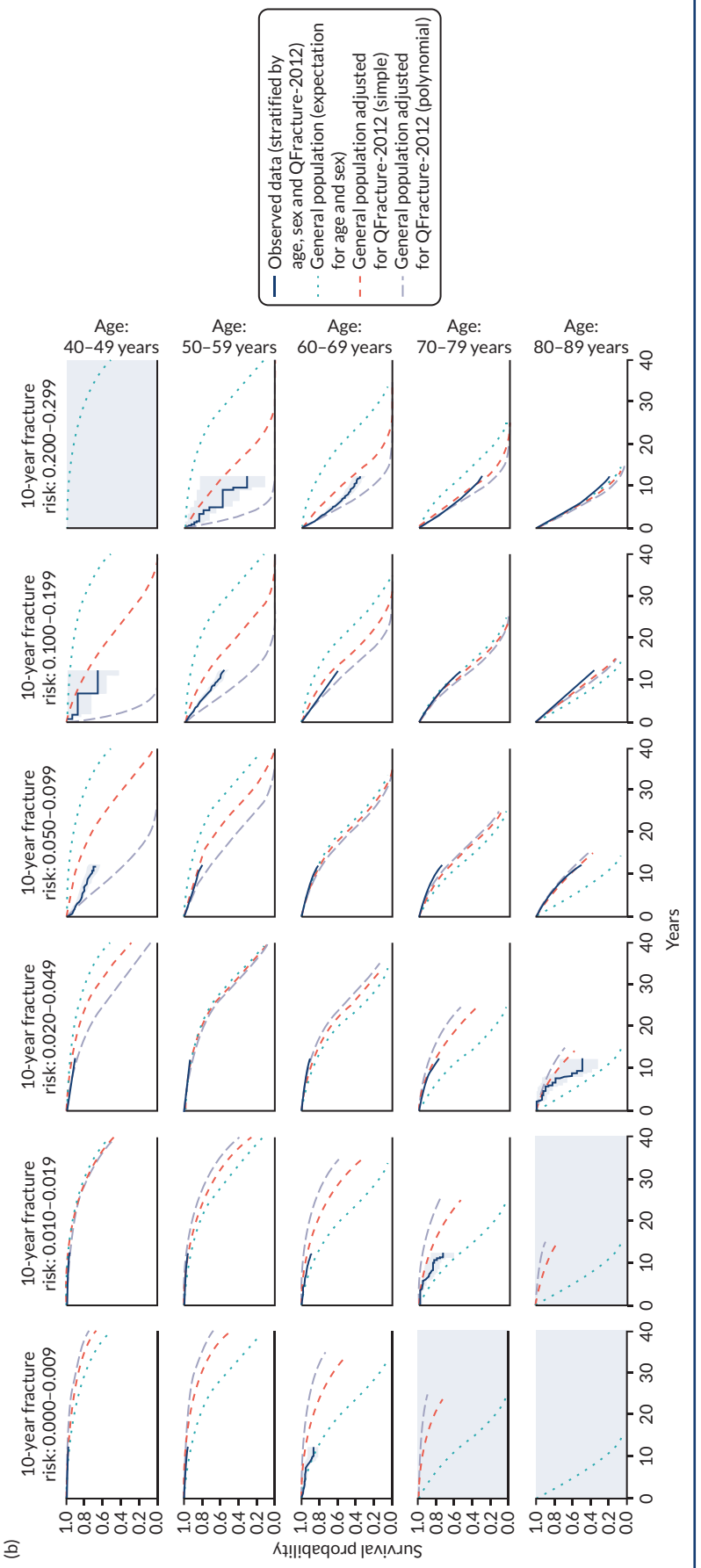


FIGURE 22 Fitted relative survival model for non-fracture mortality compared with empirical data. (a) Men; and (b) women.

To enable us to explore results further, as in TA464, we fitted a generalised additive model (GAM) to the patient-level outputs of the discrete-event model. The response variable is incremental net monetary benefit for alendronate compared with no treatment. In its simplest version, the meta-model takes the form:

$$g\left(E\left[INMB\right]\right) = \beta_0 + f\left(QFrac\right) Adj, \tag{4}$$

where $g(.)$ is a link function (i.e. identity, as we assume a Gaussian distribution for *INMB*), $f(.)$ is a smooth term (with a cubic regression spline basis function) that can capture non-linearities in the relationship between the predictor (i.e. baseline QFracture-2012 10-year serious fracture probability) and the response term, and *Adj* is a dummy variable indicating whether or not the economic model was adjusted for competing risk of non-fracture death.

We also extended the meta-modelling methods used in TA464 to provide an estimate of value for money as a function of baseline risk and age. This model takes the form:

$$g\left(E\left[INMB\right]\right) = \beta_0 + f\left(QFrac, Age\right) Adj. \tag{5}$$

Here, the joint effect of fracture risk and age becomes the target of the smooth term. As before, we stratify the model by adjustment condition.

As in previous iterations of the model,[149,150] we found that GAM predictions become erratic above a predicted 10-year fracture risk of 30%, owing to the very small numbers of simulated patients who reach this level of risk (i.e. around 0.1% of the cohort). Therefore, we fitted the meta-model to a data set excluding the few simulated people who exceed this level of risk and present only fitted results up to this threshold.

Results

Accounting for competing risk

Table 21 summarises expected events with alendronate compared with no treatment, first in the unadjusted model and then in the version that adjusts for competing risk of non-fracture death. *Table 21* presents analogous information to *Table 9* in the 2020 HTA.[149] *Table 37* of the analysis underpinning TA464[150] has something similar, although note that this is based on an uncorrected network meta-analysis, and the corrigendum does not include an updated version of the same information.[147]

Whether adjusted for competing risk or not, the updated model estimates that alendronate prevents slightly more fractures than the previous models in all categories except wrist fracture, and this is because the longer duration of treatment (and consequent extension of offset period) gives more time for the intervention to provide benefit. The reduced efficacy for wrist fracture compared with the 2020 HTA[149] is probably a result of different inputs, for example the network meta-analysis developed for the 2020 HTA[149] included a wider range of comparators and estimated a greater mean effect for bisphosphonates in preventing wrist fractures.

Comparing adjusted with unadjusted models reveals some relatively subtle differences. In higher-risk people (most obviously in the highest-risk tenth), the unadjusted model slightly overstates the effectiveness of alendronate. We can see this when we take account of the fact that people with high risk of fracture also experience increased risk of competing causes of death, with the result that fewer of people live to see the benefit of future fractures prevented. With a large enough sample, we would also expect to see the unadjusted model underpredicting fractures in the people with below-average risk (because their true life expectancy is longer than the unadjusted model simulates). There may be a hint of this type of effect in the lowest-risk tenth of the population; however, we would need a colossal sample size to detect the effect reliably, as events are so rare (and intervening deaths even rarer) in the few years during which the treatment effect obtains.

TABLE 21 Modelled effectiveness of alendronate: clinical outcomes

10-year fracture risk decile (QFracture-2012)	Events prevented per 100,000 people treated with alendronate compared with no treatment							Life-years gained per patient compared with no treatment
	Fractures						Full-time care admissions	
	Hip	Vertebral	Proximal humerus	Wrist	Fatal	Total		
Unadjusted								
1 (< 0.64%)	5	25	5	14	1	48	1	0.0000
2 (0.64–0.85%)	7	31	10	29	0	78	1	0.0001
3 (0.86–1.17%)	13	43	13	43	1	112	2	0.0002
4 (1.18–1.63%)	23	50	16	49	3	137	2	0.0006
5 (1.64–2.27%)	33	66	25	62	6	186	5	0.0007
6 (2.28–3.20%)	54	87	34	53	10	228	8	0.0010
7 (3.21–4.57%)	84	123	50	87	15	344	16	0.0021
8 (4.58–6.63%)	125	167	76	94	16	463	17	0.0020
9 (6.64–10.62%)	242	238	109	132	43	722	45	0.0035
10 (≥ 10.63%)	492	289	145	182	81	1107	112	0.0044
All	107	112	48	74	17	341	21	0.0014
Adjusted for competing risk of non-fracture death								
1 (< 0.64%)	5	27	6	15	0	53	0	0.0000
2 (0.64–0.85%)	7	31	10	28	1	76	1	0.0001
3 (0.86–1.17%)	12	45	14	41	1	111	0	0.0002
4 (1.18–1.63%)	22	49	17	49	3	137	3	0.0006
5 (1.64–2.27%)	31	64	24	57	5	177	3	0.0007
6 (2.28–3.20%)	52	83	34	54	9	223	9	0.0009
7 (3.21–4.57%)	81	118	48	83	16	331	14	0.0019
8 (4.58–6.63%)	124	163	72	94	18	452	17	0.0018
9 (6.64–10.62%)	232	227	105	116	40	680	44	0.0031
10 (≥ 10.63%)	434	252	120	151	70	956	98	0.0032
All	99	106	45	69	16	318	19	0.0012

Based on 5 million simulated people.

Table 22 shows how these dynamics translate into costs and QALYs. In absolute terms, the adjusted model generates more QALYs than the unadjusted model for people at lowest risk of fracture, and the relationship reverses as risk rises. Comparing incremental results from the unadjusted and adjusted models shows no difference in the deciles in which oral bisphosphonates represent an effective use of NHS resources. In both versions of the model, the lower-risk seven-tenths of people gain a tiny benefit from alendronate, but this benefit is insufficient to offset the additional costs associated with the intervention. Above the seventh decile, however, QALY gains get a bit larger and (because fractures cause expense to the health and care system, as well as disutility to the person) incremental costs go down, with the result that preventative treatment provides reasonable value for money (when we value QALYs at £20,000 each). In the adjusted model, the degree of net benefit expected for people at highest

TABLE 22 Cost-effectiveness results for alendronate compared with no treatment: effect of adjusting for competing risk of non-fracture death

10-year fracture risk decile (QFracture-2012)	No treatment		Alendronate		Incremental			INMB at £20,000/QALY
	Cost (£)	QALY	Cost (£)	QALY	Cost (£)	QALY	ICER (£)	
Unadjusted								
1 (< 0.64%)	735	16.6161	847	16.6164	112	0.0003	374,536	−106
2 (0.64–0.85%)	1263	15.3859	1374	15.3864	111	0.0005	226,068	−101
3 (0.86–1.17%)	2227	14.0754	2333	14.0761	106	0.0007	147,194	−91
4 (1.18–1.63%)	2833	12.7259	2937	12.7270	103	0.0011	97,309	−82
5 (1.64–2.27%)	3056	11.7241	3153	11.7255	97	0.0014	71,532	−70
6 (2.28–3.20%)	3307	10.6404	3396	10.6422	89	0.0018	49,539	−53
7 (3.21–4.57%)	3626	9.5728	3701	9.5756	75	0.0028	27,081	−20
8 (4.58–6.63%)	4381	8.4998	4435	8.5033	54	0.0035	15,460	16
9 (6.64–10.62%)	6842	6.7128	6856	6.7179	14	0.0051	2736	88
10 (≥ 10.63%)	14,632	4.2055	14,583	4.2116	−49	0.0061	Dominant	170
Adjusted for competing risk of non-fracture death								
1 (< 0.64%)	993	17.6266	1105	17.6269	112	0.0003	347,850	−106
2 (0.64–0.85%)	1354	15.7936	1466	15.7941	111	0.0005	213,695	−101
3 (0.86–1.17%)	2146	14.0179	2252	14.0186	106	0.0007	144,765	−91
4 (1.18–1.63%)	2615	12.4307	2718	12.4318	103	0.0011	97,013	−82
5 (1.64–2.27%)	2781	11.3664	2879	11.3676	98	0.0013	75,730	−72
6 (2.28–3.20%)	2979	10.2520	3068	10.2537	89	0.0017	52,834	−55
7 (3.21–4.57%)	3260	9.1986	3337	9.2012	77	0.0026	29,709	−25
8 (4.58–6.63%)	3934	8.1006	3990	8.1039	56	0.0033	17,213	9
9 (6.64–10.62%)	6117	6.2304	6137	6.2350	20	0.0046	4343	72
10 (≥ 10.63%)	12,136	3.5817	12,112	3.5863	−24	0.0046	Dominant	117

INMB, incremental net monetary benefit.

Note
Based on 5 million simulated people.

risk is discernibly lower than in the unadjusted version, and this is a direct result of the smaller number of fractures prevented, as discussed above. Nevertheless, both models agree about the people for whom incremental net benefit is positive.

Figure 23 shows the output of the GAM meta-model (see *Equation 4*) fitted to patient-level output and it is directly analogous to the green line in *Figure 3* in the corrigendum to the analysis that informed TA464[147] (with the difference that we find it helpful to show the *x*-axis on a logarithmic scale; note that the first seven deciles of risk all fit into the first sixth of the natural scale graph). This is consistent with what we have seen in previous model outputs, that is the unadjusted model overestimates benefit in people at greatest risk as, once we adjust for competing risk of other-cause death, their capacity to benefit from reduced fracture risk diminishes.

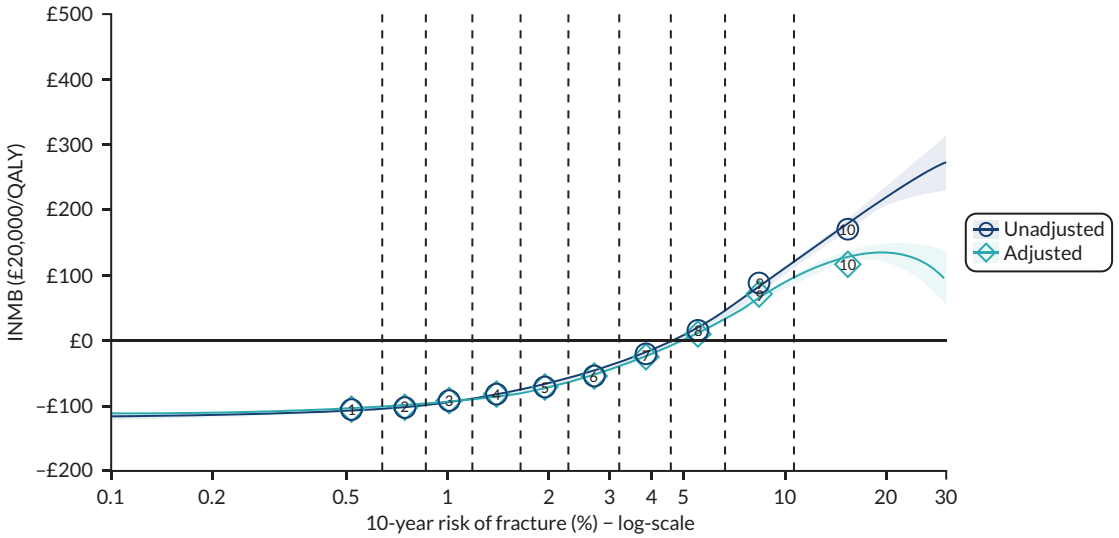


FIGURE 23 Cost-effectiveness of bisphosphonates (incremental net monetary benefit compared with no treatment) as a function of risk of fracture, with different assumptions about competing risk of non-fracture death. GAM fitted to model outputs comprising 5 million simulated patients. Lines show fitted model prediction, shaded areas show 95% CI, vertical dashed bars represent deciles of risk and numbered shapes show mean values for people within each tenth of the population (where these are missing, fewer than 100 of the total 5 million simulated people fell into the group). INMB, incremental net monetary benefit.

However, as seen before, the levels of risk at which this bias operates are almost exclusively above the point where – both adjusted and unadjusted models agree that – intervention provides positive net benefit. The unadjusted model suggests that the threshold at which alendronate becomes cost-effective is a 10-year MOF risk of 4.7 (95% CI 4.5 to 4.9), whereas the adjusted model estimates the same value as 5.0 (95% CI 4.8 to 5.2).

Extending the GAM meta-model to incorporate age as well as baseline risk (see *Equation 5*) produces outputs such as those illustrated in *Figure 24* (fitted at indicative ages of 50, 60, 70 and 80 years). By and large, results replicate those in the unstratified meta-model, that is we may overestimate value for money in people at the highest risk if we do not adjust for competing risk of non-fracture death; however, this generally only affects the magnitude of expected benefit in people for whom some degree of benefit is expected. There is some indication that these expectations may diverge for the youngest people. For example, for 50-year-olds, treatment is only cost-effective in the highest-risk tenth of people once we adjust for competing risk. Note, however, that the outputs of the meta-model are much more

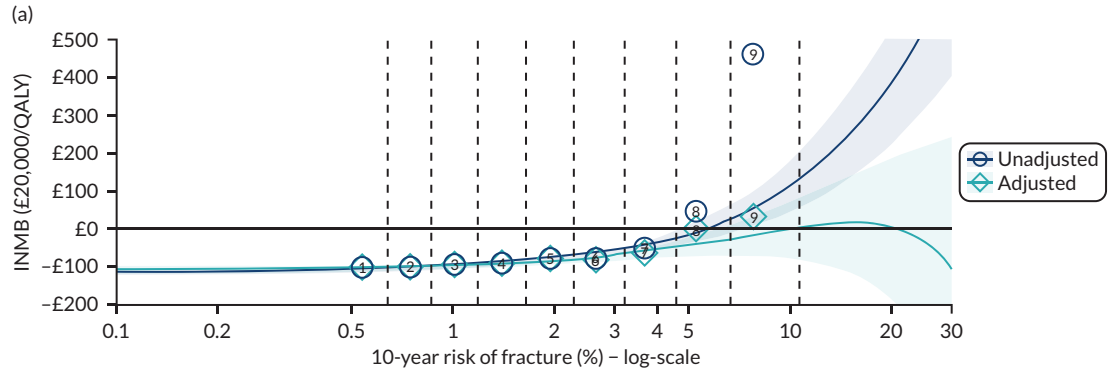


FIGURE 24 Cost-effectiveness of bisphosphonates (incremental net monetary benefit compared with no treatment) as a function of age and risk of fracture, with different assumptions about competing risk of non-fracture death. (a) Age 50 years; (b) age 60 years; (c) age 70 years: and (d) age 80 years. GAM fitted to model outputs comprising 5 million simulated patients. Lines show fitted model prediction, shaded areas show 95% CI, vertical dashed bars represent deciles of risk and numbered shapes show mean values for people within each tenth of the population (where these are missing, fewer than 100 of the total 5 million simulated people fell into the group). INMB, incremental net monetary benefit. (*continued*)

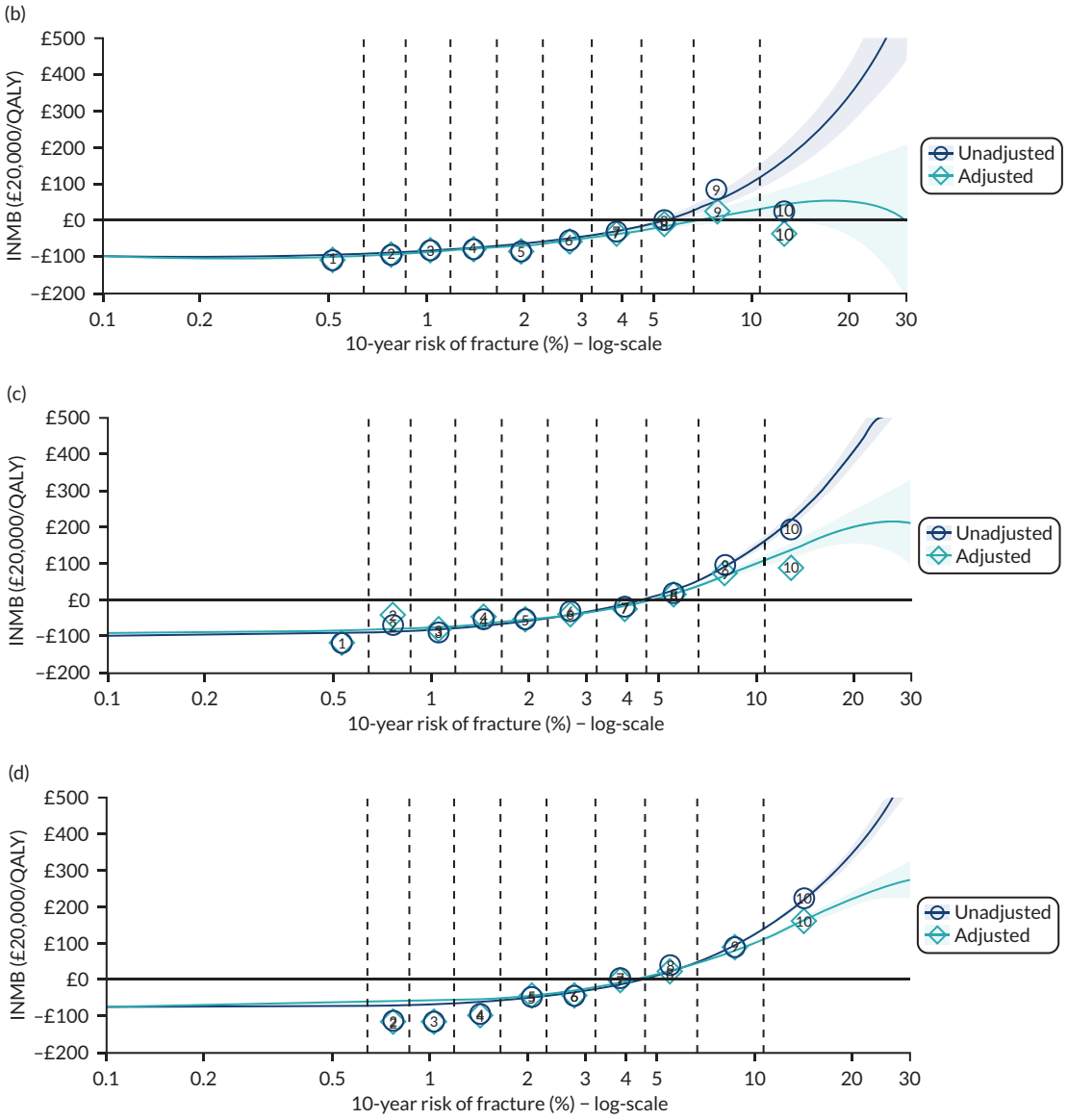


FIGURE 24 Cost-effectiveness of bisphosphonates (incremental net monetary benefit compared with no treatment) as a function of age and risk of fracture, with different assumptions about competing risk of non-fracture death. (a) Age 50 years; (b) age 60 years; (c) age 70 years: and (d) age 80 years. GAM fitted to model outputs comprising 5 million simulated patients. Lines show fitted model prediction, shaded areas show 95% CI, vertical dashed bars represent deciles of risk and numbered shapes show mean values for people within each tenth of the population (where these are missing, fewer than 100 of the total 5 million simulated people fell into the group). INMB, incremental net monetary benefit.

uncertain, in this instance, as they are based on a far smaller sample size (almost all simulated people with the highest level of fracture risk are aged > 50 years).

Appendix 9, *Table 58*, shows the threshold at which treatment becomes associated with positive net benefit according to the GAM, adjusting for age and fracture risk. Unadjusted model outputs are relatively invariant to age, whereas the adjusted model suggests that the threshold for intervention should fall as people get older (until they reach the oldest category).

As we did with the statins model, we also looked at how it would affect cost-effectiveness results if we simulated people who are fitter or less fit than average (over and above the degree that would be expected via fracture risk alone), by halving and doubling each individual's HR for non-fracture death.

Figure 25 shows results for model 2, which adjusts for fracture risk only. *Figure 26* shows the same for model 2 but adjusts for age as well. *Figure 27* shows a cross-categorisation of age and fracture risk, with varying assumptions about competing risk. As would be expected, we can see that the threshold at which intervention generates positive incremental net benefit is somewhat higher in people who are more likely to die of other things and somewhat lower in people whose increased life expectancy gives them every chance of surviving to realise the benefit of fractures prevented.

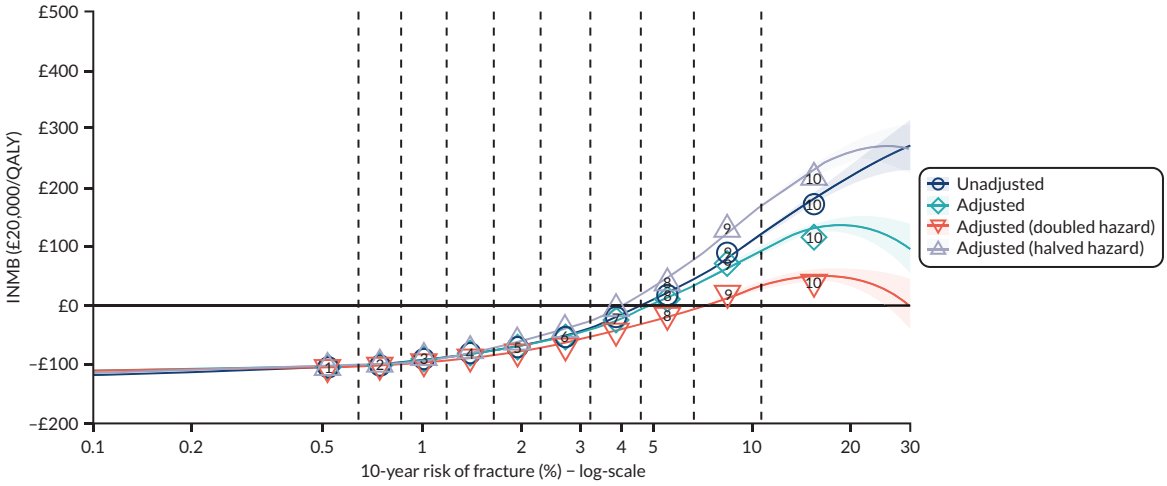


FIGURE 25 Cost-effectiveness of bisphosphonates (incremental net monetary benefit compared with no treatment) as a function of risk of fracture, with different assumptions about competing risk of non-fracture death. GAM fitted to model outputs comprising 5 million simulated patients. Lines show fitted model prediction, shaded areas show 95% CI, vertical dashed bars represent deciles of risk and numbered shapes show mean values for people within each tenth of the population (where these are missing, fewer than 100 of the total 5 million simulated people fell into the group). INMB, incremental net monetary benefit.

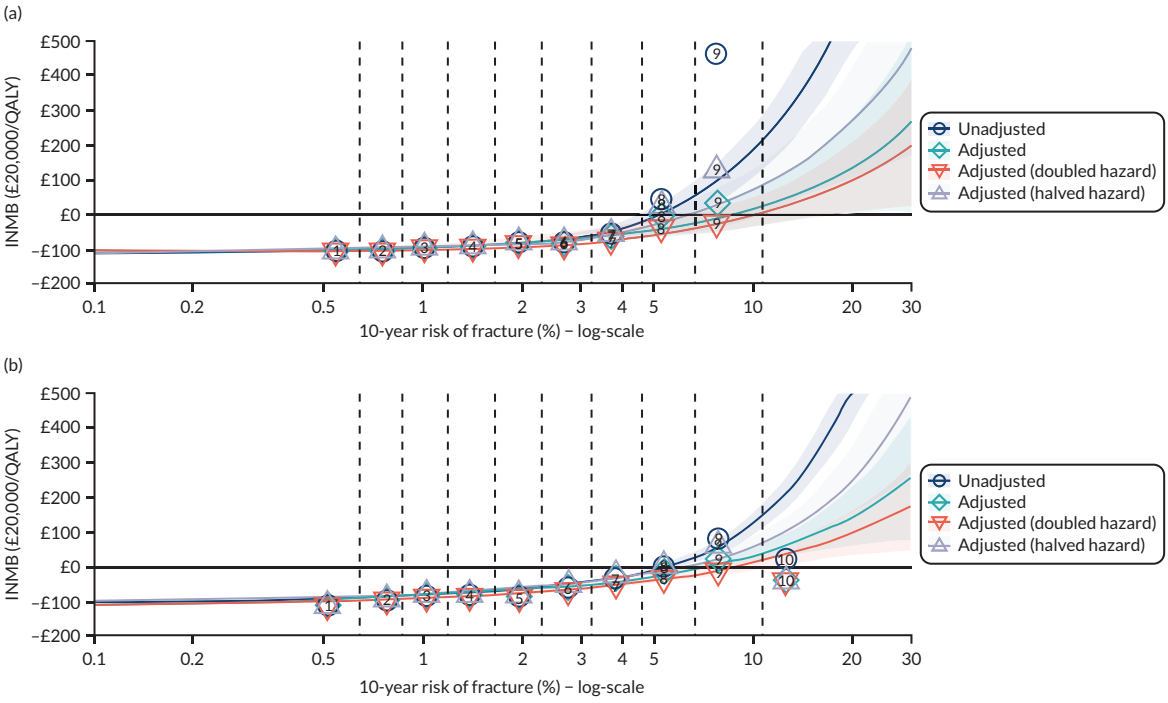


FIGURE 26 Cost-effectiveness of bisphosphonates (incremental net monetary benefit compared with no treatment) as a function of age and risk of fracture, with different assumptions about competing risk of non-fracture death. (a) Age 50 years; (b) age 60 years; (c) age 70 years; and (d) age 80 years. GAM fitted to model outputs comprising 5 million simulated patients. Lines show fitted model prediction, shaded areas show 95% CI, vertical dashed bars represent deciles of risk and numbered shapes show mean values for people within each tenth of the population (where these are missing, fewer than 100 of the total 5 million simulated people fell into the group). INMB, incremental net monetary benefit. (*continued*)

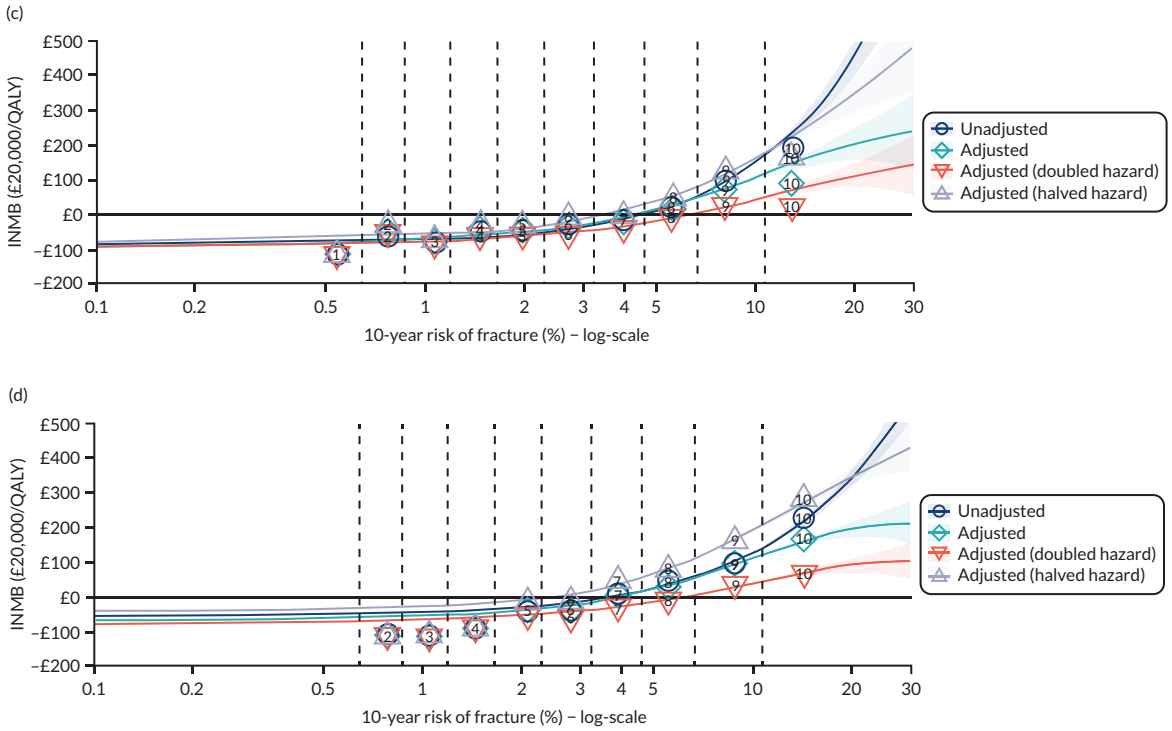


FIGURE 26 Cost-effectiveness of bisphosphonates (incremental net monetary benefit compared with no treatment) as a function of age and risk of fracture, with different assumptions about competing risk of non-fracture death. (a) Age 50 years; (b) age 60 years; (c) age 70 years; and (d) age 80 years. GAM fitted to model outputs comprising 5 million simulated patients. Lines show fitted model prediction, shaded areas show 95% CI, vertical dashed bars represent deciles of risk and numbered shapes show mean values for people within each tenth of the population (where these are missing, fewer than 100 of the total 5 million simulated people fell into the group). INMB, incremental net monetary benefit.

Incorporating direct treatment disutility

We show the lifetime discounted QALY losses we would expect from DTD in *Table 23*. Permanent and time-limited losses are identical because, in our base case, we assume that time-limited DTD lasts for 10 years and alendronate therapy is capped at 5 years. Therefore, under both scenarios, people experience full DTD for as long as they take the drug.

To give context to our estimates of DTD, we should remember that, as shown in *Table 22*, once we adjust for competing risk of non-fracture death, expected QALY gains associated with alendronate compared with no treatment are small (with no more than 0.005 QALYs per person), even in people at the highest risk of fracture. Even under the assumption of diminishing DTD, we estimate that people stand to lose more than 10 times as many QALYs from DTD as they stand to gain from the fracture-preventing effect of alendronate. Any version of *Figure 27* that also accounted for any degree of DTD would comprise exclusively black area, as there is no combination of patient characteristics that leads to expected QALY gains that come close to justifying estimated DTD.

In the competing risk-adjusted model, fewer than 0.2% of simulated people experience QALY gains that are greater than their expected DTD (in permanent, time-limited and diminishing DTD scenarios). Even in the 10% of people at highest risk of fracture, these percentages rise to only 0.53–0.58%, depending on DTD scenario, and this suggests that if DTD is present then at least 199 out of 200 people treated with bisphosphonates would experience more harm than benefit, even if their chances of fracture are high.

Even if we assume that people get used to taking bisphosphonates over a short period of 1 year, QALY losses associated with DTD are still at least five times greater than expected QALY gains. The conclusion

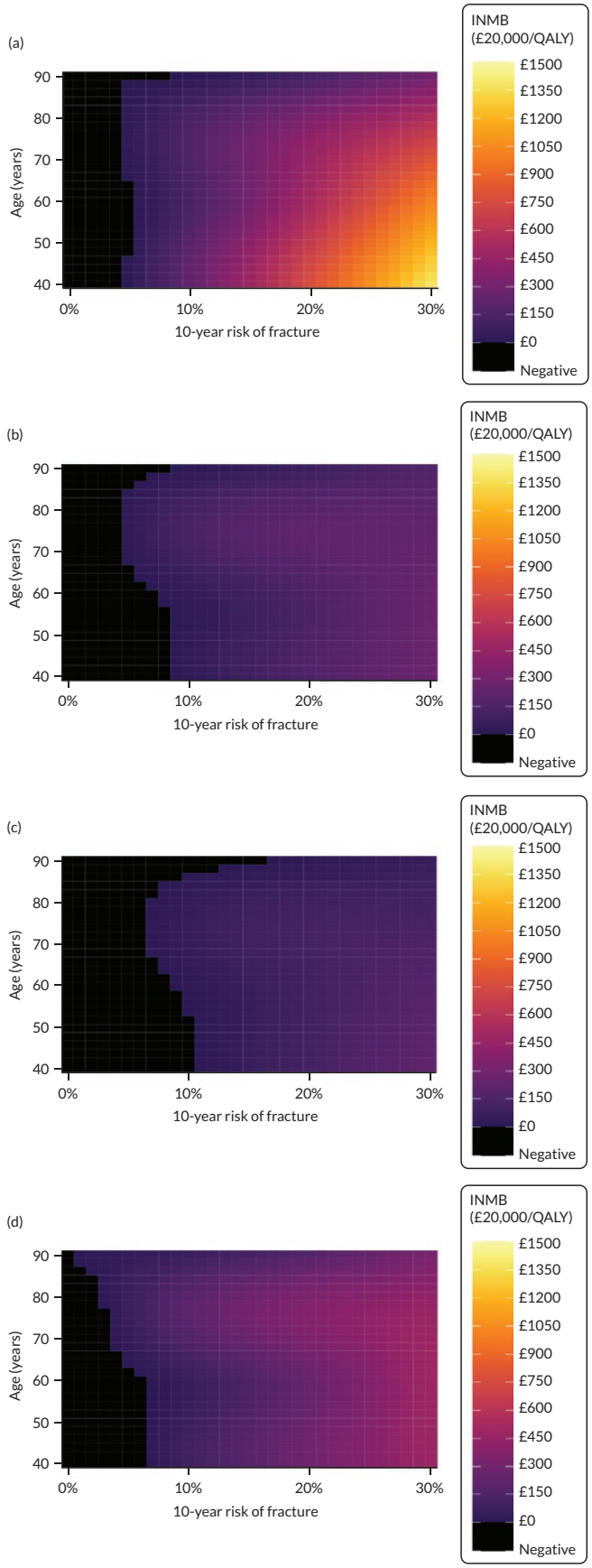


FIGURE 27 Relationship between age, risk of fracture and cost-effectiveness of bisphosphonates (incremental net monetary benefit compared with no treatment), with different assumptions about competing risk of non-fracture death. (a) Unadjusted (as per TA464); (b) adjusted for competing risk of non-fracture death; (c) adjusted with doubled hazard of non-fracture death; and (d) adjusted with halved hazard of non-fracture death. INMB, incremental net monetary benefit.

TABLE 23 Lifetime discounted QALY loss arising from DTD under various assumptions about duration of effect

10-year fracture risk decile (QFracture-2012)	Unadjusted			Adjusted for competing risk of non-fracture death		
	Permanent	Time limited	Diminishing	Permanent	Time limited	Diminishing
1 (< 0.64%)	−0.115	−0.115	−0.094	−0.116	−0.116	−0.094
2 (0.64–0.85%)	−0.116	−0.116	−0.094	−0.116	−0.116	−0.095
3 (0.86–1.17%)	−0.115	−0.115	−0.094	−0.115	−0.115	−0.094
4 (1.18–1.63%)	−0.114	−0.114	−0.094	−0.114	−0.114	−0.094
5 (1.64–2.27%)	−0.114	−0.114	−0.093	−0.113	−0.113	−0.093
6 (2.28–3.20%)	−0.113	−0.113	−0.093	−0.113	−0.113	−0.092
7 (3.21–4.57%)	−0.112	−0.112	−0.092	−0.111	−0.111	−0.092
8 (4.58–6.63%)	−0.111	−0.111	−0.091	−0.110	−0.110	−0.090
9 (6.64–10.62%)	−0.108	−0.108	−0.089	−0.106	−0.106	−0.088
10 (≥ 10.63%)	−0.101	−0.101	−0.084	−0.116	−0.116	−0.094

is inescapable: for anybody experiencing any duration of DTD of the magnitude estimated in *Chapter 5*, it is impossible to anticipate long-term benefits that would offset the up-front harm.

Discussion

Main findings

Although we would reiterate that our results should not be seen as a present-day best estimate of the cost-effectiveness of bisphosphonates, our results are closely comparable with the results generated in previous iterations of the same underlying model.[147,149,150] Alendronate is associated with small but positive net benefit in people with approximately the highest-third of fracture risk (i.e. anything above around 5% per year).

As with the cohort-level model explored in *Chapter 6*, 'adjusting for competing risk' in a discrete event simulation does not mean introducing a new concept that has, hitherto, been absent from such analyses. Rather, 'adjusting for competing risk' means taking the competing time-to-event functions the model has always simulated and ensuring that we parameterise the functions in a way that accounts for important correlations between them. We find that 'adjusting for competing risk' has a relatively subtle effect on model outputs, as it makes a small difference to the magnitude of expected benefit, but the people for whom adjustment makes the greatest absolute difference are people for whom adjusted and unadjusted models predict at least some degree of benefit. This is consistent with findings in our analysis of risk prediction models that miscalibration is often most obvious in people whose level of risk clearly exceeds intervention thresholds (see *Chapters 2–4*).

In contrast, the effects of DTD in the same decision space are anything but subtle. At the level at which we measured the effects of DTD for bisphosphonates (see *Chapter 5*), DTD of any duration would be enough to swamp expected benefit from fracture prevention. The low rates of persistence with oral bisphosphonates observed in practice are further evidence that people associate bisphosphonates with disutility of a magnitude that outweighs any anticipated gain, which lends some face validity to our findings. It follows that, once we factor cost into the equation, it is impossible to find any identifiable group of people for whom oral bisphosphonates represent an effective use of NHS resources if we assume population-level average DTD for everyone to whom the decision applies. In fact, there are a

small number of simulated people for whom bisphosphonates would be cost-effective at conventional QALY values despite these people experiencing net harm (as this can occur when non-trivial cost savings arise from prevented fractures and associated QALY gains are marginally less than DTD-related QALY losses).

Nevertheless, in the same way we argued for statins for the primary prevention of CVD (see *Chapter 6, Discussion*), we would not suggest that decision-makers should advocate blanket disinvestment in bisphosphonates. On the one hand, we think it is useful information that the average person would sacrifice more quality-adjusted life expectation to avoid taking bisphosphonates than they could expect to gain from their therapeutic effect (and this is true both of people with experience of taking bisphosphonates and members of the general public). On the other hand, although our survey respondents were more eager to avoid bisphosphonates than statins, around one-sixth of the respondents still ascribed no DTD to bisphosphonates. Therefore, if adequately informed people consider the trade-off differently to the average person (and they are at sufficiently high risk of fragility fracture to justify the costs of treatment), then we would still want to offer people access to a treatment from which they could expect some benefit before any counterweighting from disadvantages they are prepared to tolerate.

Limitations

First, our epidemiological work (see *Chapter 3*) finds that QFracture-2012 is poorly calibrated for reasons not limited to its inability to deal with competing risks, and, on the face of it, this would seem to undermine our cost-effectiveness model that, in common with its previous iterations, predicts risk of fracture using baseline QFracture-2012 predictions. However, in the world simulated by our decision-analytic model, QFracture-2012 does not have poor predictive utility but, instead, has perfect predictive utility because the model simulates events as a direct function of each simulated person's baseline risk (i.e. the simulated people in the model really do have the risk of fracture that QFracture-2012 would ascribe to them). Therefore, our results can be seen as assessing the cost-effectiveness of bisphosphonates in a population with accurate risk prediction. This means that our results would be valid for the more accurate risk estimates that a better risk prediction model would produce. The only areas in which QFracture-2012's poor calibration may undermine the model are (1) the deciles of risk by which the population is subdivided bear little relation to the true risks faced in the population and (2) for TA464, the modellers derived the distributional assumptions underpinning time-to-fracture events from analysis of QFracture-2012 data (see 'Estimating time to event from absolute fracture risk' in Davis *et al.*[150]). If a more accurate risk prediction model implied different functional forms and/or shape parameters, then this ought to be reflected in an updated cost-effectiveness model.

Second, as with our relative survival model for non-cardiovascular death, we acknowledge that collapsing risk to a single covariate (in this case, 10-year major fracture risk) runs the risk of lumping together people with different non-fracture survival expectations. For example, a 70-year-old woman with no long-term conditions but a family history of osteoporosis has an identical QFracture-2012 prediction to a 70-year-old woman with type 2 diabetes and CKD but no family history (as both have a 12.6% chance of major fragility fracture over 10 years). It is plausible that, although their risk of fracture is indistinguishable, these two profiles would be associated with markedly different life expectancy. Our relative survival model is blind to such dynamics, as the model uses fracture risk as a single covariate. When comparing our adjusted life expectancy estimates with observed data (see *Figure 22*), we acknowledge that, for some age–sex–fracture risk strata, there are larger discrepancies between modelled and observed outcomes than we saw with the cardiovascular data set. We might be able to achieve a closer fit with a more sophisticated model (i.e. instead of using a summary risk prediction measure we could estimate relative survival as a function of each of the individual covariates on which the prediction itself relies). Such an approach would theoretically be able to capture the differential effect of risk factors for fracture on life expectancy. However, this would be a very complex model to fit, and we could only validate it against ever-more stratified subsections of the empirical data, which, even when starting from a large data set, would swiftly lead to sample-size constraints. At very least, we

remain confident that our simpler modelling approach results in much better estimates of life expectancy than relying on unadjusted general population data, as has been done in all previous models.

Third, our results suggest that, after one accounts for competing risk of non-fracture death, the risk threshold for intervention with bisphosphonates goes down as people get older. This is the opposite of what is recommended in NICE Quality Standard 149 (QS149),[164] where intervention thresholds rise with age. The thresholds in QS149[164] derive from an analysis by McCloskey *et al.*,[165] the predominant aim of which was to reduce the number of people in whom treatment is indicated. Our modelling suggests that a younger person with higher risk of fracture has less capacity to benefit because they are likely to be substantially less healthy than an average person of the same age and sex, with the consequence that their life expectancy leaves less room for fracture prevention. An older person with the same estimated risk will not stand out from their contemporaries in the same way and so their life expectancy will be closer to typical.

Fourth, the modelled population has a lower proportion of people with a high fracture risk than the real population because the simulation does not account for correlations between risk factors. For example, when the model generates a simuland with type 2 diabetes, then that person is no more likely than an average member of the population to have CKD or CVD, whereas, in reality, such risk factors cluster together. This has the effect that there are unrepresentatively few people with multiple risk factors and, hence, higher fracture risk in the simulated data set. This issue may have caused or compounded the problems we encountered fitting meta-models to full data sets, leading us to truncate the data to people with predicted 10-year fracture risks lower than 30% (see *Deriving results*).

Finally, given the computational demands of producing a probabilistic sensitivity analysis, this was not possible for this study.

Conclusion

Similar to the analysis presented in *Chapter 6*, this analysis has shown that including competing risk in the model-based CEA of bisphosphonates for primary prevention produced only subtle changes to the observed cost-effectiveness. However, we noted some effect and this analysis provides more evidence that competing risk should be included in CEAs of primary prevention strategies. Incorporating DTD had a dramatic effect on the cost-effectiveness of bisphosphonates. The effect was so dramatic that the observed QALY gains from taking a bisphosphonate were swamped by DTD in all scenarios. This result raises an interesting challenge to decision-makers in the context of bisphosphonates. However, rather than advise bisphosphonates should not be recommended because of the possible DTD, we advise that the impact of including DTD in sensitivity analyses on the outputs of a decision-analytic model should be an integral component of CEAs of primary prevention strategies.

Chapter 8 Summary and conclusions

Summary of findings

The overall aim was to improve the evidence generated from risk prediction models and model-based CEAs to inform decision-making for selecting primary prevention treatments for CVD and osteoporotic fracture.

In *Chapter 2*, we showed that QRISK3 had excellent discrimination and good calibration in the whole population of people aged 25–84 years when ignoring competing mortality risks. However, QRISK3 overpredicted somewhat in the whole population when accounting for competing risks, and had poor to moderate discrimination and calibration (with larger overprediction) in important subgroups, including older people, those with multimorbidity and people with diabetes or CKD. Overprediction was worse at higher levels of predicted CVD risk, but there was some overprediction at the 10-year 10% risk threshold currently recommended by NICE as defining who to offer statins to for primary prevention. Accounting for competing risk in derivation of new models (CRISK and CRISK-CCI) improved calibration, although discrimination was very similar to QRISK3 (which, in part, reflects that excellent discrimination in QRISK3 is primarily driven by the inclusion of a very large range of age).

Chapter 3 found that QRISK-Lifetime (evaluated with a 10-year prediction horizon) had excellent discrimination but systematic underprediction in the whole population. Discrimination was worse in all age strata, and progressively worse with increasing age and increasing comorbidity. In all age strata there was evidence of underprediction, which increased with increasing age. The systematic underprediction of 10-year risk by QRISK-Lifetime implies that lifetime risk will be underestimated. Lifetime risk prediction and QRISK3 10-year risk prediction recommended largely non-overlapping groups for treatment, with QRISK-Lifetime recommending younger people who were more likely to have a strong family history and be smokers for treatment. However, over 10 years, people recommended for statin treatment based on lifetime risk experienced considerably fewer CVD events, meaning that treatment based on lifetime risk evaluation requires a leap of faith that currently observed CVD incidence rates in older people will be maintained.

In *Chapter 4*, QFracture-2012 was found to have two important problems. First, QFracture-2012 underpredicted fracture risk in general, partly because its derivation used only GP and mortality data to define fracture outcomes (although other differences must reflect either better recording of fracture in more recent data and/or differences in the codesets used to ascertain fracture). Second, competing mortality risk had a much larger impact than for CVD, reflecting that osteoporotic fracture is a relatively rare cause of sudden death, and this led to overprediction in general, which was very large in older people and people with multimorbidity. Accounting for competing risk in derivation of new models (CFracture) to predict major osteoporotic and hip fracture improved calibration, although, again, discrimination was very similar to QFracture-2012. Although CFracture performed better, neither QFracture-2012 nor CFracture predicted fracture risk well in people aged 85–99 years.

The stated-preference surveys reported in *Chapter 5* demonstrated that most people think the inconvenience of taking statins or bisphosphonates is not negligible. In the TTO exercise, most respondents would be prepared to forgo some life expectancy to avoid taking either pill, although it was clear that participants consider statins less bothersome than bisphosphonates. Consistent with previous studies, our findings suggest that, although most people perceive a benefit–harm trade-off, some people would avoid taking the medicines at all costs and some people foresee zero disutility. We explored the same issues in a BWS experiment, which had face validity in that inconvenience influenced preferences. However, the DTD values we have so far been able to calculate from the BWS data appear implausibly large.

As noted in *Chapters 6* and *7*, decision-analytic models of the type used for NICE CEAs are structurally fit to account for competing risks as a matter of course. However, the parameterisation of time to death seldom accounts for the fact that, in many cases, people who are at higher risk of condition-specific events will also be at higher risk of other-cause mortality. Our relative survival models address this problem by estimating the extent to which predicted condition-specific risk explains divergence from expected population mortality. Applying these estimates in our updated decision-analytic models has the expected effect, that is people with below-average condition-specific risk for their sex and age accrue more QALYs (because they experience lower other-cause mortality) and people with above-average condition-specific risk end up with fewer QALYs (because their other-cause life expectancy is attenuated). This phenomenon was observable in the statins model, but it had little impact on incremental cost–utility results, mostly because the model suggests that statins provide net benefit for almost everyone (and our updates made this conclusion even stronger). In the bisphosphonates model, the main impact of accurate adjustment for competing risk of non-fracture death is to attenuate expected value for money in people at highest risk of fracture. However, this generally affects the magnitude of expected net benefit in only people for whom some degree of benefit is expected. Introducing DTD to the equation has a more obvious effect in both models. For statins, if we assume that DTD applies for a prolonged period or permanently, then intervention would be net harmful for younger people at lower risk of CVD, with the risk threshold rising as people get older. However, treatment remains net beneficial for most people at higher risk of CVD. For bisphosphonates, DTD of any duration would be enough to swamp expected benefit from fracture prevention. Therefore, we are unable to find any identifiable group of people for whom oral bisphosphonates represent an effective use of NHS resources, if we assume population-level average DTD for everyone to whom the decision applies.

Implications of findings for policy and practice

A first implication is that excellent discriminative performance of clinical risk prediction tools in the entire population is not enough to conclude that a tool performs well. In this study, all risk prediction tools examined (including our own) had excellent discrimination in the whole population, but typically poor to moderate discrimination when stratified by age and moderate to good discrimination when stratified by comorbidity level. For age, this is expected because age is part of the risk equation and age is the dominant predictor of risk.[72] Put another way, however, it is relatively easy to have good discrimination when the population studied has a ≥ 60-year age range (and clinicians have little problem identifying that a 30-year-old has much lower risk of CVD or fracture than an 80-year-old). Any clinical risk prediction tool that includes such a wide age range is, therefore, likely to have good to excellent discrimination, but that does not mean that the tool will be that effective in discriminating people of similar ages. Equally, using discrimination to compare risk prediction tools that include very different age ranges will often be misleading.[100] Calibration is a better guide to prediction tool performance, but the same issue applies (i.e. good calibration in the whole population does not necessarily mean good calibration in key subgroups). Therefore, guideline developers need to carefully consider discrimination and calibration in the populations they are making recommendations for, and prediction tool developers and validators should publish age-stratified evaluations of tool performance (although we recognise that this can be limited by having too few events in some subgroups).

Second, ignoring competing mortality risks led to overprediction of risk by QRISK3 and QFracture-2012. As fractures are a rare cause of immediate death (unlike CVD where a fair proportion of CVD events are sudden death), the impact of this was much greater for QFracture-2012 than for QRISK3, with QFracture-2012 additionally predicting risk in people aged up to 99 years compared with up to 84 years for QRISK3. For QRISK3, overprediction mostly (but not entirely) happened above the NICE recommended 10-year 10% risk threshold (although overprediction would have had greater impact for the long period when NICE and others recommended a 20% threshold). For QFracture-2012, thresholds are less well defined, but overprediction was very large in older people (i.e. people aged 85–99 years)

and people with high levels of comorbidity at the highest fracture risk (despite QFracture-2012 in general underpredicting).

Our new competing risk models, which are essentially adaptations of QRISK3 and QFracture-2012, were better calibrated than QRISK3 and QFracture. For the moment, clinicians should consider wider life expectancy related to other conditions when discussing long-term cardiovascular and fracture primary preventative treatment. However, when new competing risk models are externally validated (a requirement before clinical use), and assuming that the performance of the new models is good enough, they should be used to inform clinical practice. However, irrespective of which prediction model is used, clinicians need to use judgement in making treatment recommendations based on discussion and shared decision-making with the patient, including consideration of individual preferences, life expectancy and comorbidity.[166]

Third, we found serious problems with the calibration of QFracture-2012, but this has since been replaced by a new version which (like this study) ascertains fractures using both GP and hospital data.[167] The observed under-ascertainment of QFracture-2012 in this study is therefore likely to be less for the current version of QFracture but we would expect competing mortality to remain a major problem.

Of note, the FRAX fracture risk prediction tool is also recommended by NICE and does account for competing mortality risk, but its calibration has not been well studied in external validation.[22,91] The same Israeli study used to externally validate QFracture-2012 also examined FRAX, finding similar levels of underprediction as was found for QFracture-2012 (although the analysis did not account for competing mortality risk).[92] However, FRAX risk prediction in Dagan *et al.*'s[92] study was limited to broad categorisation of FRAX-estimated risk, reflecting the failure of the FRAX developers to make the prediction algorithm publicly available and, therefore, replicable. Although FRAX does account for competing mortality risk, it remains uncertain how well calibrated a tool it is in the UK (or any other) context. Publication of the full algorithm would allow direct and fair comparison with other tools to identify the optimal tool for different contexts;[92] however, for now, we do not think it can be recommended for use either.[21]

Fourth, we have demonstrated that the relative survival models derived from the clinical data used in the risk prediction modelling provide an effective method of adjusting for competing risk of non-cause-specific death that modellers can easily apply in decision-analytic CEAs. Although the adjustment made relatively little difference to the estimated cost-effectiveness of preventative interventions in the examples we explored, we have shown that it could potentially be important in cases where benefits, harms and costs are more finely balanced. Therefore, we recommend that modellers consider competing risks when designing analyses of preventative treatments.

Finally, present-day policy-makers work under the assumption that, except inasmuch as they are associated with specific adverse events, people consider the act of taking oral treatments benign. Our stated-preference surveys, in conjunction with emerging evidence from elsewhere,[47,48,103] show clearly that this is untrue. When incorporated in CEA, we see than DTD not only exists, but it also has the potential to alter the balance of benefits and harms for many or all people for whom preventative treatments might otherwise be indicated.

Nevertheless, as argued in *Chapter 5*, we do not recommend that population-level average DTD is incorporated in base-case CEAs, and this is because we have found evidence that there is clear heterogeneity in elicited DTD, with a non-trivial proportion of people unbothered by the prospect of taking pills. We believe that it would be invidious to deny such people access to treatment by assuming that they share the average person's aversions. Therefore, we recommend that population-level decision-makers review scenarios with and without DTD and highlight the possible effects of DTD, enabling prescribers to engage in shared decision-making at an individual level that gives appropriate weight to each person's preferences for avoiding the treatment's process characteristics. A practical

implication for prescribers is to recognise that patients with strong preferences against medicine-taking may well not realise long-term net benefit in terms of quality of life, which supports an approach to decision-making that focuses on concordance (where necessary, agreeing to disagree), rather than compliance or adherence (where there is more scope for conflict as clinicians try to persuade patients to accept the clinical recommendation). We have argued that this approach fits well with NICE's guideline development methods, which encourage the explicit identification of 'preference-sensitive decision-points', taking the practicalities of possible treatments into account.[125]

Implications of findings for research

There are several areas where further research would be beneficial:

- In this study, the observed impact of competing mortality risks varied between CVD and fracture prediction tools, and it would be useful to explore the implications of accounting for competing mortality for prediction tools in other clinical contexts (although there is a strong case that all risk prediction tools intended for use in older people and people with multimorbidity should account for competing risks by default, or clearly justify why not).
- A feature of both QRISK3 and QFracture-2012 is that they are 'omnibus' models predicting risk across a very wide range of ages and morbidities. It is unclear if this is a sensible approach, or whether or not subgroup models developed specifically for older adults or (in the case of CVD) people with diabetes would be a better strategy. A major disadvantage of subgroup models is that an individual might belong to multiple subgroups, for example being an older adult with diabetes and CKD; however, for diabetes at least, QRISK3 appears very poorly calibrated in external validation using diabetes registry data.[60,76] One reason for the difference between validation in registry data and the validation carried out here is that the inclusion criteria for QRISK3 derivation and validation effectively removes a large number of people with diabetes from the data set because of prior statin exposure. This has three implications for research. First, more attention needs to be paid to exactly who the derivation and validation populations are, as differences between studies will sometimes be explained by this. Second, primary prevention treatments are often very widely prescribed and so models (like QRISK3, but unlike QFracture-2012) that exclude people with prior drug exposure become increasingly unrepresentative. For blood pressure, QRISK3 fits both current SBP and a term for whether or not the person is on antihypertensive treatment, and this may be a better strategy for statin prescribing as well. Third, although it is likely that subgroup models will perform somewhat better than omnibus models, subgroup models may not perform that much better (if at all) to be worth the additional cost of developing a myriad of models for different circumstances, and relative performance is a researchable question.
- In the fracture analysis, both QFracture-2012 and CFracture were poorly calibrated in people aged 85–99 years. In this particular case, that may be because fracture risk in younger people is more driven by characteristics associated with osteoporosis, whereas in older people it may be more driven by characteristics associated with falls risk that are not well recorded in routine data (e.g. balance, sarcopenia and frailty). More broadly, however, most risk prediction excludes the very old, and there is a need for research to examine risk prediction in the very old who are the fastest growing segment of the UK population. In this context, established risk factors may be less relevant because, for example, high cholesterol is clearly not associated with premature vascular disease in 95-year-olds without vascular disease, and where multimorbidity means that tools that predict multiple events would be ideal to inform treatment choice in the face of concerns about polypharmacy and treatment burden.[5,166] Research is needed to explore such issues, and the value of risk factor treatment in older people with comorbidity and co-prescribing who are routinely excluded from trials could be usefully clarified with targeted randomised controlled trials.[3]
- A feature of the data sets used to derive and validate QRISK3 and QFracture-2012 are that they have more limited follow-up than is generally appreciated (typically a median of 5–7 years' follow-up). This study has examined the impact of competing risk, but other loss to follow-up due to practice

deregistration is likely to create overprediction in at least some population subsets (e.g. people who deregister to move to sheltered housing or care homes are very likely to have different outcomes to those who do not). External validation in large geographical populations with less loss to follow-up (e.g. the SAIL Databank in Wales) would be valuable, as would larger-scale data federation to derive and validate new risk prediction tools for comparison with QRISK3 and other prediction models.

- The tools examined here and most other risk prediction tools use only clinical data. In principle, polygenic risk scores using genetic data combined with key environmental exposures, like smoking, could identify people with high lifetime risk earlier than any clinical risk prediction tool. More research is needed to understand the value of such additional predictors; however, in some cases, risk prediction may be superseded or complemented by better diagnostics. In CVD, for example, lifetime risk prediction is an attempt to deal with the problem that younger people at high risk of premature CVD often do not have 10-year CVD risk that exceeds current threshold for treatment. Lowering 10-year risk thresholds might mitigate this problem, but lead to very large proportions of people being recommended for lifelong medication that most will not benefit from (and, in any case, many people will not wish to take lifelong treatment based on risk prediction alone). An alternative strategy is to screen people for asymptomatic coronary artery disease using computerised tomography coronary angiography, and to then treat the people with disease rather than people at risk of the disease. For CVD at least, early diagnosis and treatment may be an attractive strategy, given the problems of risk prediction over long periods of time. This strategy of early diagnosis and treatment has been shown to be effective in people with chest pain,[168] but its value in a true primary prevention population is uncertain and needs to be established.[105,106]
- The results from the BWS method to estimate DTD should be anchored to a credible absolute estimate to generate plausible values on a utility scale that could be used in CEA. There was a TTO embedded within our BWS exercise that could perform this function, and exploring this TTO to derive results that are more directly comparable with the dedicated TTO exercise is a priority for future work.
- We have suggested ways in which DTD can be used to augment CEA in this project. However, there is no consensus about which values are most appropriate (e.g. general population valuations vs. valuations by people with experience of the interventions) and how values should be applied in analysis (e.g. for how long should we assume effects last) and deployed in decision-making (e.g. should population-level decision-makers recommend technologies that are rendered net harmful if population-level average DTD applies?). Few of these issues are amenable to empirical research, but we would like to see consensus-building work to establish best practice.
- Although we have substantially improved the model NICE used in CG181 to assess statins for the primary prevention of CVD [e.g. by estimating transition probabilities using the same UK data set (CPRD) used in the risk prediction modelling], it was not within our remit to update every input, and there are some respects in which it could usefully be further modified. In particular, we think it would be valuable to (1) explore stratification according to specific co-existing long-term conditions, (2) account for likely adherence to statins in practice and (3) update secondary transitions reflecting the treated history of CVD in people experiencing events.
- Similarly, we have noted several areas in which there is room to improve future CEAs of bisphosphonates for the primary prevention of osteoporotic fragility fracture. As a priority, researchers should explore alternatives to QFracture-2012 to predict fracture risk, which, as shown in *Chapter 4*, suffers from under-ascertainment of events. We argue in *Chapter 7* that inaccuracy of risk prediction tools does not, in itself, invalidate the results of the bisphosphonates CEA; however, it would clearly be desirable to integrate a tool with better predictive performance into such analyses. We also note that the simulated population on which the TA464 model bases its calculations is unrealistic because, when generating virtual people, the model samples each characteristic independently. Introducing evidence on correlations between risk factors would produce a more realistic cohort and may minimise the problem we (and the TA464 modellers) encountered where outputs seem unstable for people at the highest levels of risk.

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Study Advisory Group

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Ethics

The literature elements of the study did not require ethics review. The prediction modelling used CPRD data and the protocol was approved by the CPRD Independent Scientific Advisory Committee (reference number 16_248). The DTD elicitation study was reviewed by the Health Research Authority (Integrated Research Application System project ID 220,492) and granted ethics approval (Research Ethics Committee reference 17/NW/0124).

Contributions of authors

Bruce Guthrie (https://orcid.org/0000-0003-4191-4880) (Professor of General Practice, The University of Edinburgh) was the overall chief investigator, contributed to the conceptualisation, conduct and interpretation of the study, co-ordinated the writing of the report, led the writing of *Chapters 1*–*4* and *8*, and wrote elements of *Chapters 5*–*7*.

Gabriel Rogers (https://orcid.org/0000-0001-9339-7374) (Senior Research Fellow in Health Economics, The University of Manchester) contributed to the conduct and interpretation of the study, led the writing of *Chapters 6* and *7*, co-wrote *Chapter 4*, and provided comment on and editing of the report.

Shona Livingstone (https://orcid.org/0000-0002-4621-8713) (Statistician, University of Dundee) was the employed researcher in Dundee, contributed to the conduct and interpretation of the study, and provided comment on and editing of the report.

Daniel Morales (https://orcid.org/0000-0002-0063-8069) (Wellcome Trust Clinical Research Career Development Fellow, University of Dundee) contributed to the conceptualisation, conduct and interpretation of the study, and provided comment on and editing of the report.

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Livingstone S, Morales DR, Donnan PT, Payne K, Thompson AJ, Youn JH, *et al*. Effect of competing mortality risks on predictive performance of the QRISK3 cardiovascular risk prediction tool in older people and those with comorbidity: external validation population cohort study. *Lancet Healthy Longev* 2021;**2**:e352–61. https://doi.org/10.1016/S2666-7568(21)00088-X

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Data-sharing statement

The data used in the risk prediction modelling are controlled by the CPRD, and under the data licence granted the authors are not allowed to share the data. Researchers can apply to CPRD directly for access to the raw data. For the health economics modelling, the parameters of the models are all fully documented in this final report and the documents it cites, and there are no additional data to share. If you have any further queries, please contact the corresponding author.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 QRISK3 external validation, and CRISK and CRISK-CCI derivation and internal validation

TABLE 24 Missing data in the CVD data set

Data	How missingness was handled in analysis	Women		Men	
		External validation cohort (*N* = 1,484,597), *n* (%) missing data	QRISK3 internal validation cohort (*N* = 1,360,457), *n* (%) missing data	External validation cohort (*N* = 1,420,176), *n* (%) missing data	QRISK3 internal validation cohort (*N* = 1,310,841), *n* (%) missing data
BMI	Imputed	409,464 (27.6)	363,705 (26.7)	590,513 (41.6)	458,320 (35.0)
TC : HDL	Imputed	1,260,807 (84.9)	817,195 (60.1)	1,207,422 (85.0)	809,236 (61.7)
SBP	Imputed	252,064 (17.0)	214,418 (15.8)	489,276 (34.5)	387,874 (29.6)
SBP variability	Imputed	695,935 (46.9)	287,790 (21.2)	1,051,621 (74.0)	497,468 (38.0)
Smoking status	Imputed	300,216 (20.2)	191,525 (14.1)	443,494 (31.2)	275,416 (21.0)
Ethnicity	Assumed white	309,747 (20.9)	510,760 (37.5)	504,698 (35.5)	559,471 (42.7)
Complete data for BMI, TC : HDL, SBP, smoking status and ethnicity[a]	N/A	170,056 (11.5)	389,774 (28.7)	153,779 (10.8)	330,073 (25.2)
Age	Never missing	0	0	0	0
Sex	Never missing	0	0	0	0
Socioeconomic status	Excluded	2796 (0.2%)[b]	0.4% of all patients[c]	2671 (0.2%)[b]	0.4% of all patients[c]
Conditions and prescribing variables	Assumed to be absent if no record	N/A	N/A	N/A	N/A

N/A, not applicable.
a Not included in model (individual variables are included separately ± interaction terms).
b Patients with missing Townsend score were excluded before cohort creation.
c QRISK3 derivation paper[25] reported for the whole population only and not by gender.

TABLE 25 Adjusted subdistribution HRs for CVD in women in the derivation cohort for CRISK-CCI

Predictor	Subdistribution HR (95% CI)
$(\text{Age in years}/10)^{0.5} - 2.1163$	65.8 (51.5 to 83.9)
$(\text{BMI}/10)^{2} - 7.0332$	1.03 (1.02 to 1.05)
(SBP/10) – 12.5032	1.11 (1.06 to 1.16)
log(TC : HDL) – 1.2069	1.47 (1.28 to 1.67)
$(\text{Townsend score} + 3.8101)^{0.5} - 1.620{,}811$	1.31 (1.19 to 1.44)
Variance in SBP – 9.5910	1.01 (1.01 to 1.02)
Atrial fibrillation	4.98 (2.52 to 9.83)
Atypical antipsychotics	1.09 (0.71 to 1.68)
Corticosteroid use	2.16 (1.40 to 3.26)
Migraine	1.50 (1.21 to 1.86)
Rheumatoid arthritis	1.31 (1.01 to 1.69)
CKD (stage 3, 4 or 5)	1.79 (0.59 to 5.43)
Serious mental illness	1.22 (1.06 to 1.40)
SLE	1.74 (0.60 to 4.98)
Treated hypertension	1.48 (1.13 to 1.94)
Type 1 diabetes	2.69 (1.29 to 5.58)
Type 2 diabetes	2.19 (1.30 to 3.71)
Family history of CHD in first-degree relative < 60 years	1.27 (1.02 to 1.59)
Smoking status	
Non-smoker	1
Former smoker	1.32 (1.07 to 1.63)
Light smoker	2.05 (1.65 to 2.54)
Moderate smoker	2.25 (1.82 to 2.79)
Heavy smoker	2.62 (2.10 to 3.28)
Ethnicity	1
Indian, Pakistani or Bangladeshi	1.53 (1.10 to 2.12)
Other Asian	1.14 (0.47 to 2.76)
Black Caribbean or Black African	0.97 (0.61 to 1.52)
Other	1.07 (0.77 to 1.49)
CCI	
0	1
1	1.22 (1.11 to 1.34)
2	1.11 (0.96 to 1.29)
≥ 3	1.18 (0.94 to 1.49)
Interactions with age term	
Age term – atrial fibrillation	0.22 (0.08 to 0.63)
Age term – corticosteroid use	0.38 (0.17 to 0.81)
Age term – migraine	0.60 (0.35 to 1.01)

TABLE 25 Adjusted subdistribution HRs for CVD in women in the derivation cohort for CRISK-CCI (*continued*)

Predictor	Subdistribution HR (95% CI)
Age term – CKD	0.46 (0.07 to 3.18)
Age term – treated hypertension	0.73 (0.46 to 1.15)
Age term – type 1 diabetes	0.61 (0.14 to 2.63)
Age term – type 2 diabetes	0.43 (0.17 to 1.07)
Age term – family history of CHD	0.81 (0.45 to 1.44)
Age term – former smoker	0.84 (0.57 to 1.24)
Age term – light smoker	0.67 (0.44 to 1.03)
Age term – moderate smoker	0.55 (0.35 to 0.87)
Age term – heavy smoker	0.44 (0.26 to 0.73)
Age term – BMI term	0.97 (0.94 to 1.00)
Age term – SBP term	0.92 (0.85 to 0.99)
Age term – Townsend term	0.71 (0.59 to 0.85)
Age term – SLE	0.88 (0.06 to 12.2)

CHD, coronary heart disease; CIF, cumulative incidence function; SLE, systemic lupus erythematosus.

Note
Baseline 10-year CIF of 0.712,743%, corresponding to the following baseline characteristics: aged 44.8 years, BMI of 26.5 kg/m^2, SBP of 125 mmHg, TC : HDL of 3.3 mmol/l, Townsend score of −1.183, variance in BP of 9.6 mmHg, white or assumed white ethnicity, non-smoker and none of the individual conditions in the model.

TABLE 26 Adjusted subdistribution HRs for CVD in men in the derivation cohort for CRISK-CCI

Predictor	Subdistribution HR (95% CI)
$(\text{Age in years}/10)^{-0.5} - 0.4888$	7.66×10^{-10} (2.05×10^{-10} to 2.87×10^{-9})
(BMI/10) – 2.6514	1.29 (1.14 to 1.46)
(SBP/10) – 13.0309	1.12 (1.07 to 1.16)
log(TC : HDL) – 1.4124	1.54 (1.37 to 1.74)
$(\text{Townsend score} + 3.8101)^{0.5} - 1.6479$	1.20 (1.10 to 1.30)
$(\text{Variance in SBP} + 0.0001)^{-0.5} - 1.6701$	1.00 (1.00 to 1.00)
Atrial fibrillation	3.92 (1.71 to 8.98)
Atypical antipsychotics	1.12 (0.78 to 1.60)
Corticosteroid use	1.82 (1.12 to 2.98)
Impotence	1.25 (0.87 to 1.80)
Migraine	1.48 (1.12 to 1.97)
Rheumatoid arthritis	1.19 (0.85 to 1.68)
CKD (stage 3, 4 or 5)	2.13 (1.19 to 3.80)
Serious mental illness	1.22 (1.04 to 1.44)
SLE	0.381 (0.05 to 3.06)
Treated hypertension	1.70 (1.28 to 2.25)
Type 1 diabetes	2.17 (0.71 to 6.70)

continued

TABLE 26 Adjusted subdistribution HRs for CVD in men in the derivation cohort for CRISK-CCI (*continued*)

Predictor	Subdistribution HR (95% CI)
Type 2 diabetes	1.87 (1.11 to 3.15)
Family history of CHD in first-degree relative < 60 years	1.64 (1.32 to 2.02)
Smoking status	
Non-smoker	1
Former smoker	1.11 (0.93 to 1.33)
Light smoker	1.84 (1.48 to 2.29)
Moderate smoker	2.01 (1.68 to 2.42)
Heavy smoker	2.59 (2.19 to 3.06)
Ethnicity	1
Indian, Pakistani or Bangladeshi	1.75 (1.30 to 2.36)
Other Asian	1.58 (0.92 to 2.71)
Black Caribbean or Black African	0.71 (0.46 to 1.10)
Other	1.17 (0.89 to 1.53)
CCI	
0	1
1	1.17 (1.07 to 1.28)
2	1.19 (1.02 to 1.38)
≥ 3	1.17 (0.93 to 1.46)
Interactions with age term	
Age term – atrial fibrillation	2.92 (2.17 to 3.93 × 10^6)
Age term – impotence	20.1 (0.18 to 2.21 × 10^3)
Age term – corticosteroid use	3.71 (0.07 to 192)
Age term – migraine	9.65 (0.28 to 336)
Age term – CKD	259 (1.40 to 4.81 × 10^4)
Age term – treated hypertension	21.4 (1.45 to 314)
Age term – type 1 diabetes	2.77 (2.23 × 10–7 to 3.42 × 10^7)
Age term – type 2 diabetes	31.5 (0.24 to 4.14 × 10^3)
Age term – family history of CHD	13.7 (0.73 to 256)
Age term – former smoker	1.73 (0.265 to 11.3)
Age term – light smoker	17.6 (1.5 to 207)
Age term – moderate smoker	44.2 (5.19 to 376)
Age term – heavy smoker	120 (14.9 to 961)
Age term – BMI term	3.51 (0.891 to 13.8)
Age term – SBP term	1.48 (0.953 to 2.29)
Age term – Townsend term	2.71 (1.1 to 6.67)

CHD, coronary heart disease; SLE, systemic lupus erythematosus.

Note
Baseline 10-year CIF of 1.3133%, corresponding to the following baseline characteristics: aged 41.9 years, BMI of 26.5 kg/m^2, SBP of 130 mmHg, TC : HDL of 4.1 mmol/l, Townsend score of −1.095, variance in SBP of 0.4 mmHg, white or assumed white ethnicity, non-smoker and none of the above conditions.

TABLE 27 Baseline data in external validation cohort and in original QRISK3 internal validation cohort[4]

Data	Women		Men	
	External validation cohort (*N* = 1,484,597)	Original QRISK3 internal validation cohort (*N* = 1,360,457)	External validation cohort (*N* = 1,420,176)	Original QRISK3 internal validation (*N* = 1,310,841)
Age (years), mean (SD)	46.0 (15.3)	43.3 (15.3)	44.8 (13.9)	42.6 (13.8)
BMI (kg/m^2), mean (SD)	25.9 (5.7)	25.4 (5.1)	26.6 (4.7)	25.9 (4.2)
TC : HDL (mmol/l), mean (SD)	3.7 (1.1)	3.6 (1.2)	4.4 (1.3)	4.4 (1.3)
SBP (mmHg), mean (SD)	125.4 (18.0)	123.1 (18.1)	131.1 (16.2)	128.8 (16.2)
SBP variability (mmHg), mean (SD)	10.0 (5.7)	9.3 (6.1)	10.3 (6.2)	9.9 (6.8)
Ethnicity, *n* (%)				
White or not recorded	1,363,146 (91.8)	1,218,391 (89.6)	1336,221 (94.1)	1,171,281 (89.4)
Indian	22,488 (1.5)	23,146 (1.7)	15,322 (1.1)	26,479 (2.0)
Pakistani	9550 (0.6)	10,919 (0.8)	6647 (0.5)	14,787 (1.1)
Bangladeshi	2594 (0.2)	8738 (0.6)	2145 (0.2)	11,914 (0.9)
Other Asian	13,697 (0.9)	17,078 (1.3)	9973 (0.7)	15,966 (1.2)
Black Caribbean	9505 (0.6)	13,142 (1.0)	6687 (0.5)	10,642 (0.8)
Black African	18,804 (1.3)	27,678 (2.0)	12,822 (0.9)	25,251 (1.9)
Chinese	6739 (0.5)	8992 (0.7)	3503 (0.2)	6098 (0.5)
Other	38,074 (2.6)	32,373 (2.4)	26,829 (1.9)	28,423 (2.2)
Smoking status, *n* (% of non-missing)				
Non-smoker	707,774 (59.8)	706,671 (51.9)	478,671 (49.0)	512,252 (39.1)
Former smoker	217,404 (18.4)	194,545 (14.3)	216,883 (22.2)	196,459 (15.0)
Light smoker	85,277 (7.2)	154,565 (11.4)	75,260 (7.7)	177,693 (13.6)
Moderate smoker	111,690 (9.4)	74,933 (5.5)	112,411 (11.5)	84,914 (6.5)
Heavy smoker	62,236 (5.3)	38,218 (2.8)	93,457 (9.6)	64,107 (4.9)
Family history of CHD in first-degree relative aged < 60 years, *n* (%)	97,624 (6.6)	164,023 (12.1)	75,237 (5.3)	123,039 (9.4)
Type 1 diabetes, *n* (%)	3752 (0.3)	3351 (0.2)	4843 (0.3)	3932 (0.3)
Type 2 diabetes, *n* (%)	17,022 (1.1)	15,872 (1.2)	21,077(1.5)	19,318 (1.5)
Treated hypertension, *n* (%)	115,944 (7.8)	77,694 (5.7)	82,768 (5.8)	56,920 (4.3)
Rheumatoid arthritis, *n* (%)	12,702 (0.9)	15,139 (1.1)	4724 (0.3)	7055 (0.5)
Atrial fibrillation, *n* (%)	8199 (0.6)	5229 (0.4)	10,620 (0.7)	6874 (0.5)

continued

TABLE 27 Baseline data in external validation cohort and in original QRISK3 internal validation cohort[4] (*continued*)

Data	Women		Men	
	External validation cohort (*N* = 1,484,597)	Original QRISK3 internal validation cohort (*N* = 1,360,457)	External validation cohort (*N* = 1,420,176)	Original QRISK3 internal validation (*N* = 1,310,841)
CKD (stage 3, 4 or 5), *n* (%)	6918 (0.5)	6949 (0.5)	5659 (0.4)	4232 (0.3)
Migraine, *n* (%)	117,692 (7.9)	89,504 (6.6)	41,471 (2.9)	36,141 (2.8)
Corticosteroid use, *n* (%)	20,674 (1.4)	31,775 (2.3)	11,824 (0.8)	18,634 (1.4)
HIV/AIDS, *n* (%)	289 (0.02)	1595 (0.1)	445 (0.03)	2945 (0.2)
SLE, *n* (%)	1725 (0.1)	1349 (0.1)	165 (0.01)	134 (0.0)
Atypical antipsychotic use, *n* (%)	8469 (0.6)	6268 (0.5)	8336 (0.6)	6597 (0.5)
Severe mental illness, *n* (%)	110,799 (7.5)	94,724 (7.0)	57,264 (4.0)	57,830 (4.4)
Erectile dysfunction diagnosis or treatment, *n* (%)	N/A	N/A	39,264 (2.8)	31,136 (2.4)

AIDS, acquired immunodeficiency syndrome; CHD, coronary heart disease; HIV, human immunodeficiency virus; N/A, not applicable; SD, standard deviation; SLE, systemic lupus erythematosus.

TABLE 28 Incidence rates of CVD per 1000 person-years

Age group (years)	Women				Men			
	Number of incident cases	Person-years of follow-up	Rate per 1000 person-years (95% CI)	QRISK3 derivation:[25] rate per 1000 person-years (95% CI)[a]	Number of incident cases	Person-years of follow-up	Rate per 1000 person-years (95% CI)	QRISK3 derivation:[25] rate per 1000 person-years (95% CI)[a]
25–29	257	942,262	0.3 (0.2 to 0.3)	0.3 (0.22 to 0.26)	313	903,432	0.3 (0.3 to 0.4)	0.4 (0.38 to 0.42)
30–34	560	1,153,862	0.5 (0.4 to 0.5)	0.5 (0.47 to 0.52)	974	1,144,138	0.9 (0.8 to 0.9)	1.0 (0.95 to 1.02)
35–39	1098	1,238,221	0.9 (0.8 to 0.9)	1.0 (0.99 to 1.10)	2185	1,249,707	1.7 (1.7 to 1.8)	2.1 (2.1 to 2.2)
40–44	1762	1,136,909	1.5 (1.5 to 1.6)	1.9 (1.8 to 2.0)	3519	1,145,201	3.1 (3.0 to 3.2)	4.0 (3.9 to 4.1)
45–49	2221	939,971	2.4 (2.3 to 2.5)	3.2 (3.1 to 3.3)	4779	916,468	5.2 (5.1 to 5.4)	6.6 (6.5 to 6.7)
50–54	2739	812,590	3.4 (3.2 to 3.5)	4.8 (4.7 to 4.9)	5628	749,133	7.5 (7.3 to 7.7)	9.9 (9.7 to 10.0)
55–59	3776	754,370	5.0 (4.8 to 5.2)	7.5 (7.4 to 7.6)	6877	654,761	10.5 (10.3 to 10.8)	14.2 (14.0 to 14.4)
60–64	4053	509,885	7.9 (7.7 to 8.2)	11.4 (11.2 to 11.5)	6249	409,070	15.3 (14.9 to 15.7)	19.7 (19.5 to 19.9)
65–69	4864	387,189	12.6 (12.2 to 12.9)	17.1 (16.9 to 17.4)	6126	289,067	21.2 (20.7 to 21.7)	26.6 (26.2 to 26.9)
70–74	6169	304,427	20.3 (19.8 to 20.8)	25.1 (24.8 to 25.4)	6157	207,295	29.7 (29.0 to 30.4)	35.5 (35.0 to 35.9)
75–80	7117	237,437	30.0 (29.3 to 30.7)	35.1 (34.7 to 35.5)	5758	142,794	40.3 (39.3 to 41.4)	45.2 (44.5 to 45.8)
80–84	7835	177,496	44.1 (43.2 to 45.1)	48.0 (47.4 to 48.7)	4501	85,637	52.6 (51.1 to 54.1)	58.3 (57.2 to 59.4)
Total	42,451	8,594,620	4.94 (4.9 to 5.0)	6.2 (6.16 to 6.22)	53,066	7,896,704	6.72 (6.66 to 6.78)	8.2 (8.14 to 8.21)

a In the QRISK3 derivation and internal validation paper,[25] the quoted rates are reported to be per 1000 patient-years but are actually per 100 patient-years (i.e. are all stated as 10 times higher than shown here, but calculate to these values).

TABLE 29 Discrimination and model fit in people with diabetes

Diabetes type	Harrell's *c*-statistic (95% CI)	D-statistic (95% CI)	R^2-statistic (95% CI)
Type 1			
Women	0.830 (0.768 to 0.891)	2.11 (1.80 to 2.43)	51.6 (43.7 to 58.4)
Men	0.853 (0.803 to 0.902)	1.97 (1.73 to 2.20)	48.0 (41.7 to 53.6)
Type 2			
Women	0.741 (0.722 to 0.760)	1.31 (1.22 to 1.41)	29.2 (26.2 to 32.1)
Men	0.695 (0.679 to 0.712)	1.09 (1.00 to 1.17)	22.0 (19.4 to 24.6)

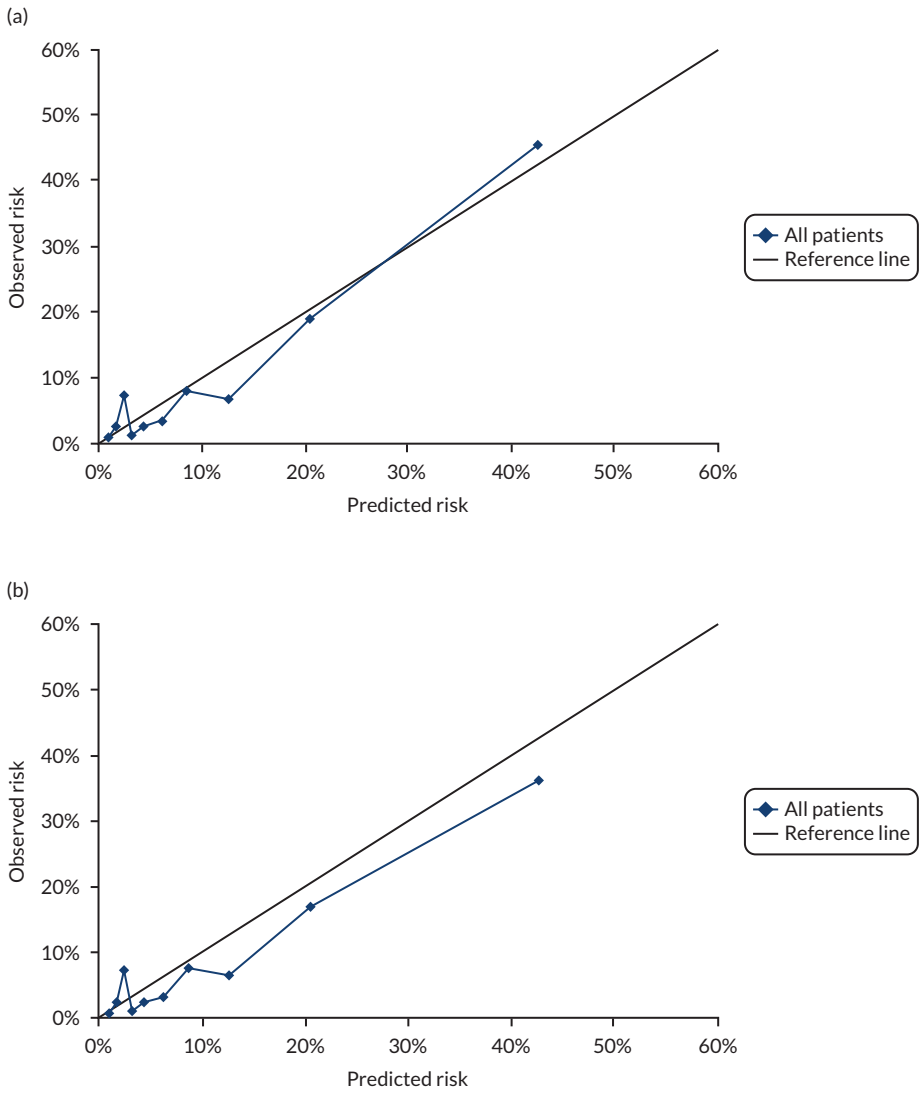

FIGURE 28 Calibration in type 1 diabetes. (a) Women with type 1 diabetes not accounting for competing risks;[a] (b) women with type 1 diabetes accounting for competing risks;[b] (c) men with type 1 diabetes not accounting for competing risks;[a] and (d) men with type 1 diabetes accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. (*continued*)

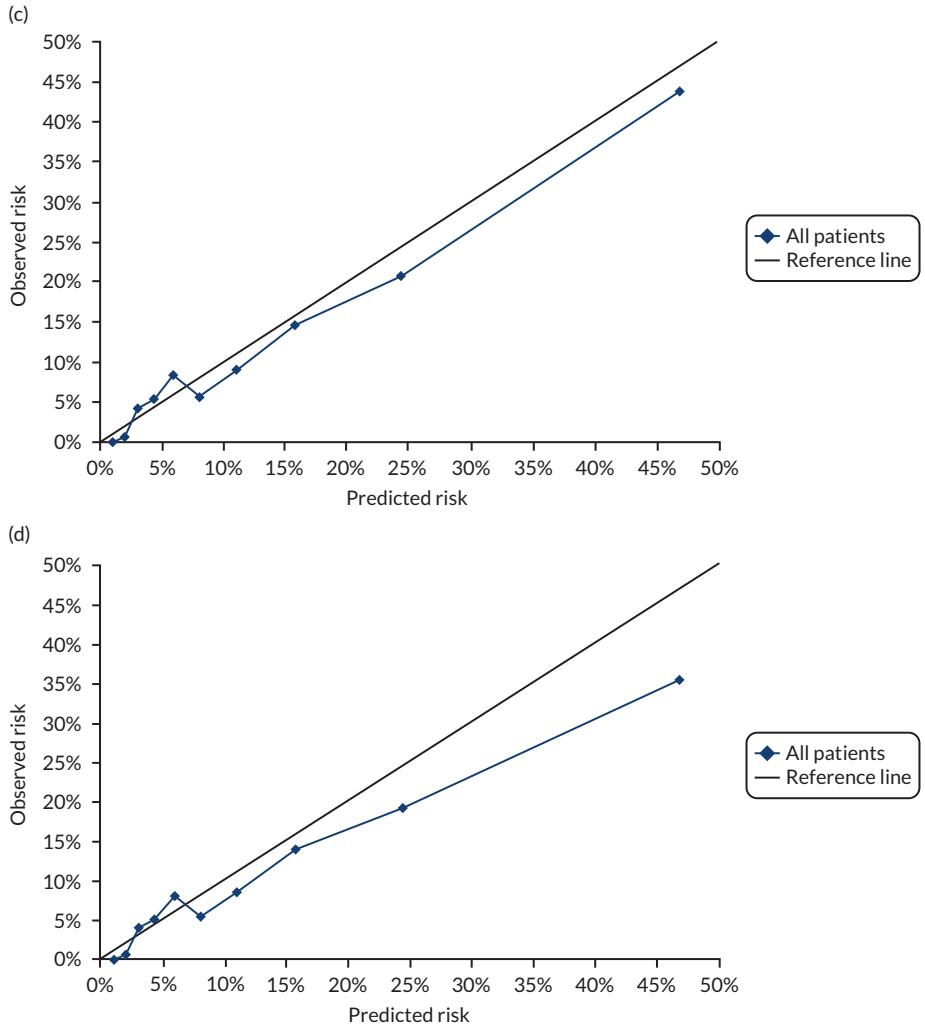

FIGURE 28 Calibration in type 1 diabetes. (a) Women with type 1 diabetes not accounting for competing risks;[a] (b) women with type 1 diabetes accounting for competing risks;[b] (c) men with type 1 diabetes not accounting for competing risks;[a] and (d) men with type 1 diabetes accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk.

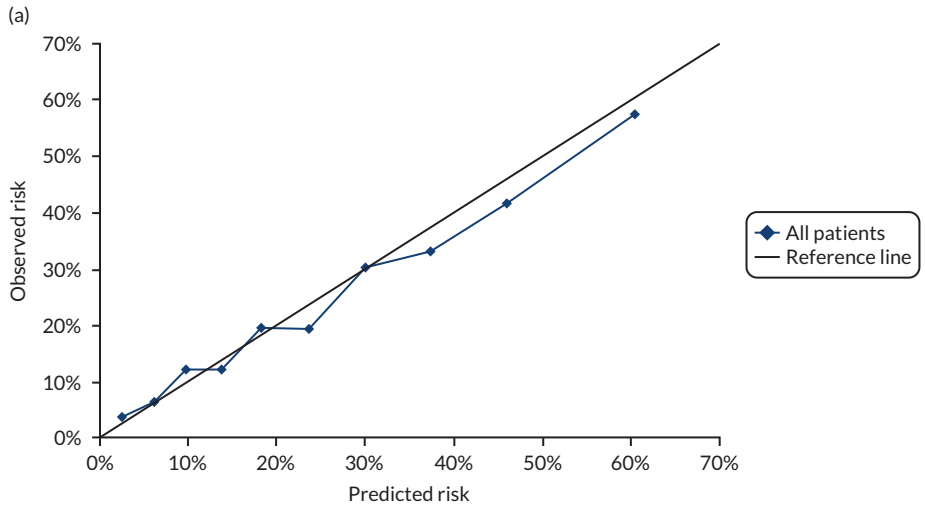

FIGURE 29 Calibration in type 2 diabetes. (a) Women with type 2 diabetes not accounting for competing risks;[a] (b) women with type 2 diabetes accounting for competing risks;[b] (c) men with type 2 diabetes not accounting for competing risks;[a] and (d) men with type 2 diabetes accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. (*continued*)

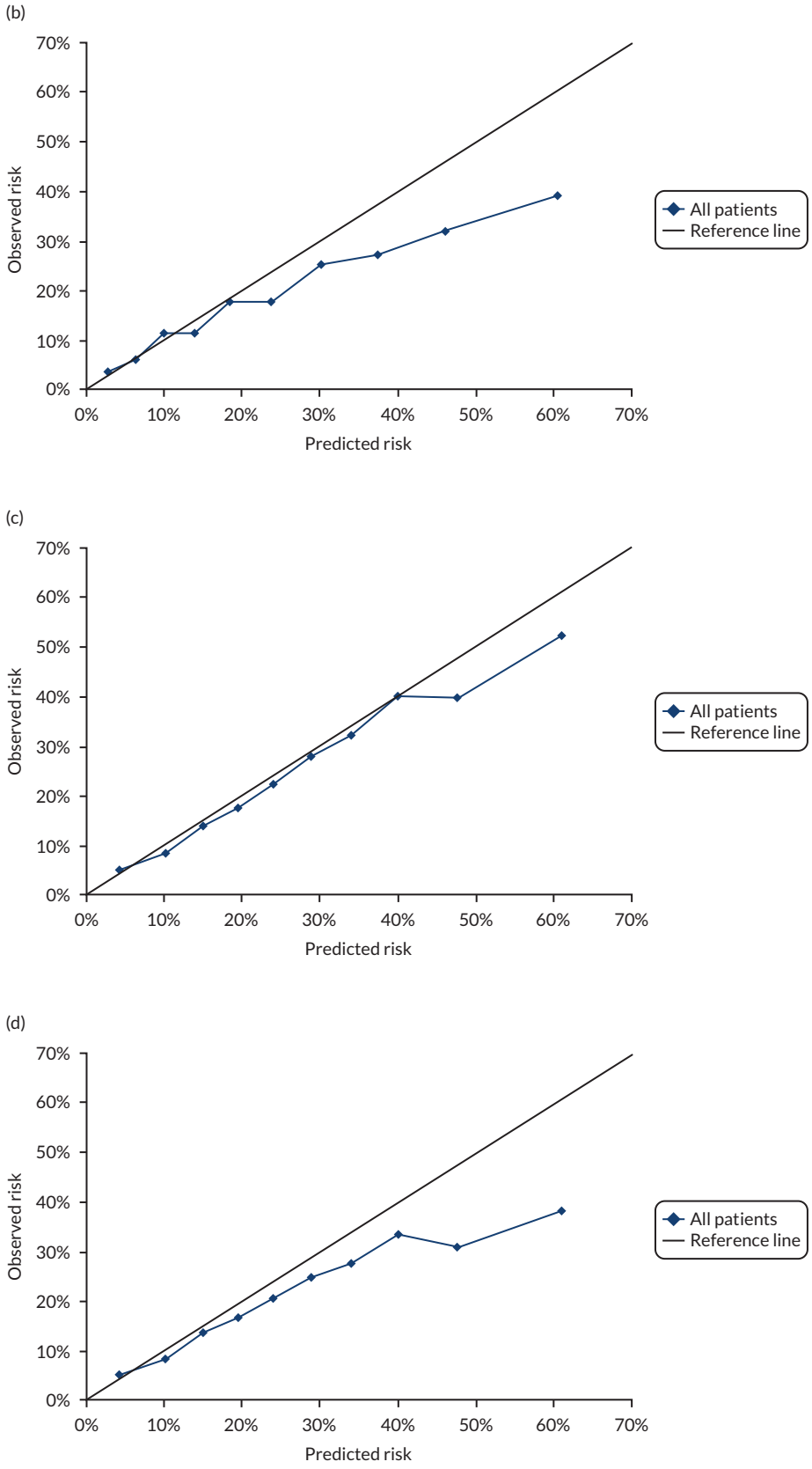

FIGURE 29 Calibration in type 2 diabetes. (a) Women with type 2 diabetes not accounting for competing risks;[a] (b) women with type 2 diabetes accounting for competing risks;[b] (c) men with type 2 diabetes not accounting for competing risks;[a] and (d) men with type 2 diabetes accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk.

TABLE 30 Discrimination and model fit in people with CKD

CKD	Harrell's *c*-statistic (95% CI)	D-statistic (95% CI)	R^2-statistic (95% CI)
CKD Read code[a]			
Women	0.755 (0.728 to 0.782)	1.47 (1.34 to 1.61)	34.2 (29.9 to 38.3)
Men	0.734 (0.708 to 0.760)	1.33 (1.19 to 1.47)	29.7 (25.4 to 34.0)
CKD Read code or eGFR[b]			
Women	0.705 (0.699 to 0.712)	1.18 (1.14 to 1.22)	24.9 (23.7 to 26.2)
Men	0.671 (0.663 to 0.680)	0.94 (0.89 to 0.99)	17.4 (15.8 to 18.9)

a CKD Read code is CKD defined using only Read codes as per the QRISK3 derivation.[25]
b CKD Read code or eGFR is CKD defined by either Read code or last recorded eGFR of < 60 ml/minute.

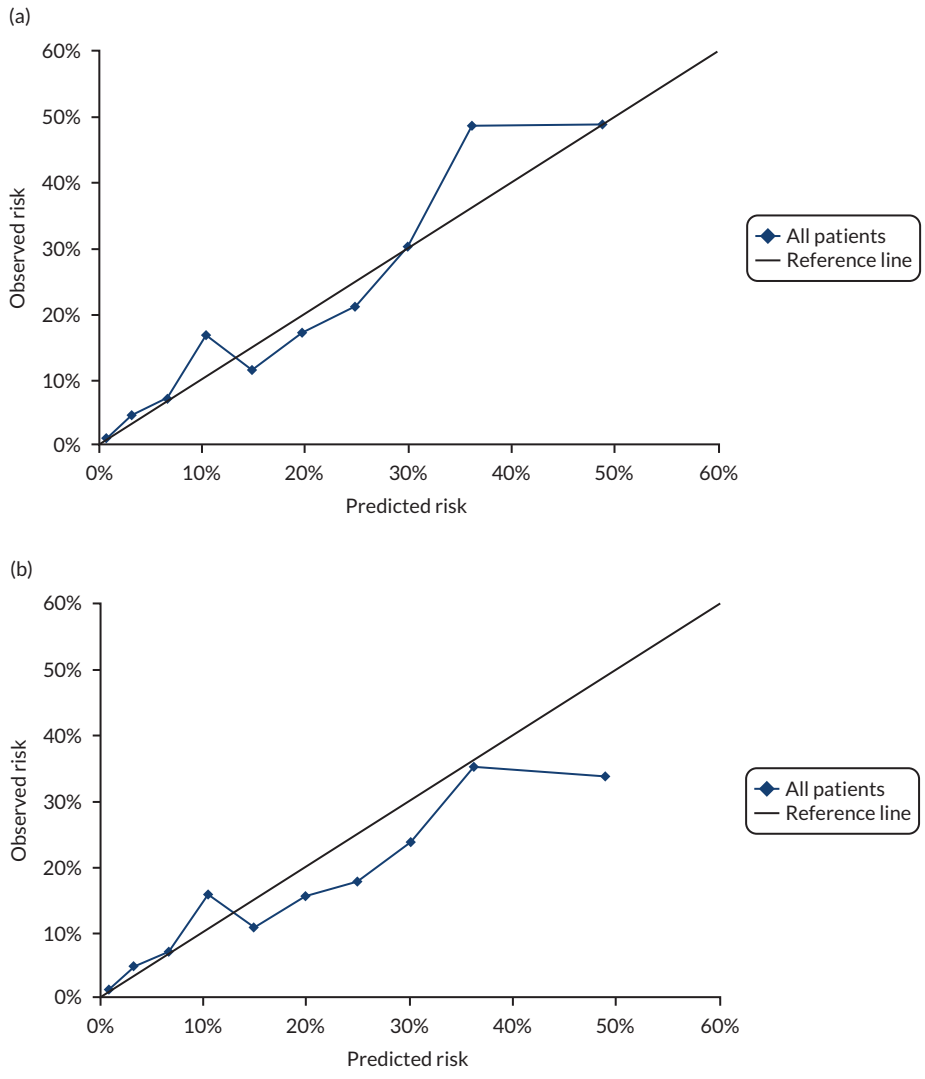

FIGURE 30 Calibration in people with CKD defined by Read code. (a) Women with CKD defined by Read code not accounting for competing risks;[a] (b) women with CKD defined by Read code accounting for competing risks;[b] (c) men with CKD defined by Read code not accounting for competing risks;[a] and (d) men with CKD defined by Read code accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. (*continued*)

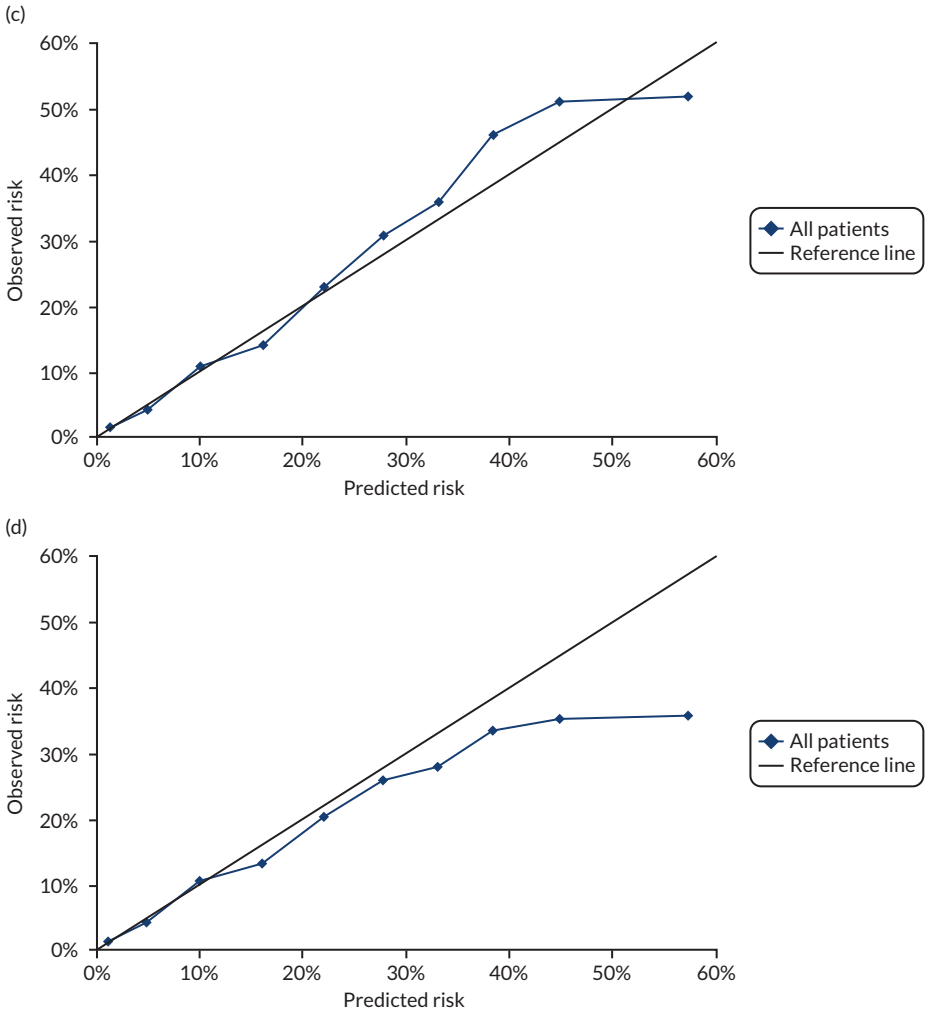

FIGURE 30 Calibration in people with CKD defined by Read code. (a) Women with CKD defined by Read code not accounting for competing risks;[a] (b) women with CKD defined by Read code accounting for competing risks;[b] (c) men with CKD defined by Read code not accounting for competing risks;[a] and (d) men with CKD defined by Read code accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk.

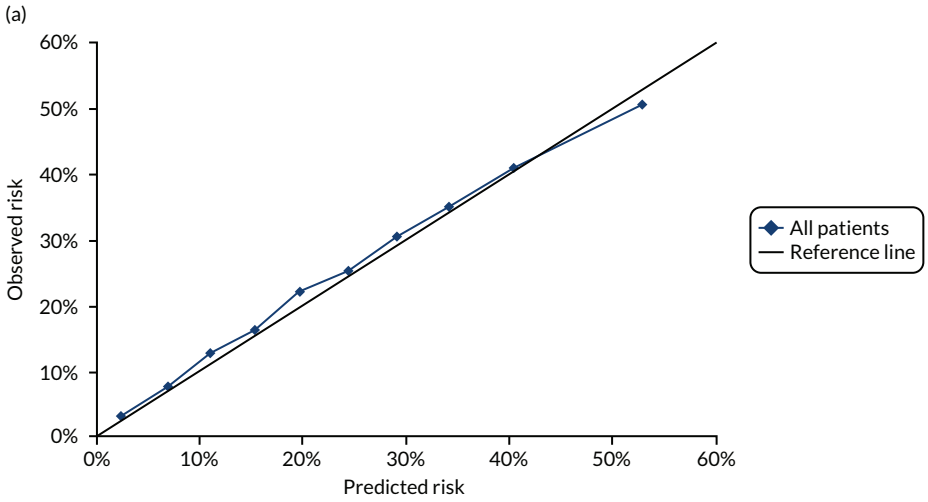

FIGURE 31 Calibration in CKD defined by Read code and eGFR. (a) Women with CKD defined by Read code or eGFR not accounting for competing risks;[a] (b) women with CKD defined by Read code or eGFR accounting for competing risks;[b] (c) men with CKD defined by Read code or eGFR not accounting for competing risks;[a] and (d) men with CKD defined by Read code or eGFR accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk. (*continued*)

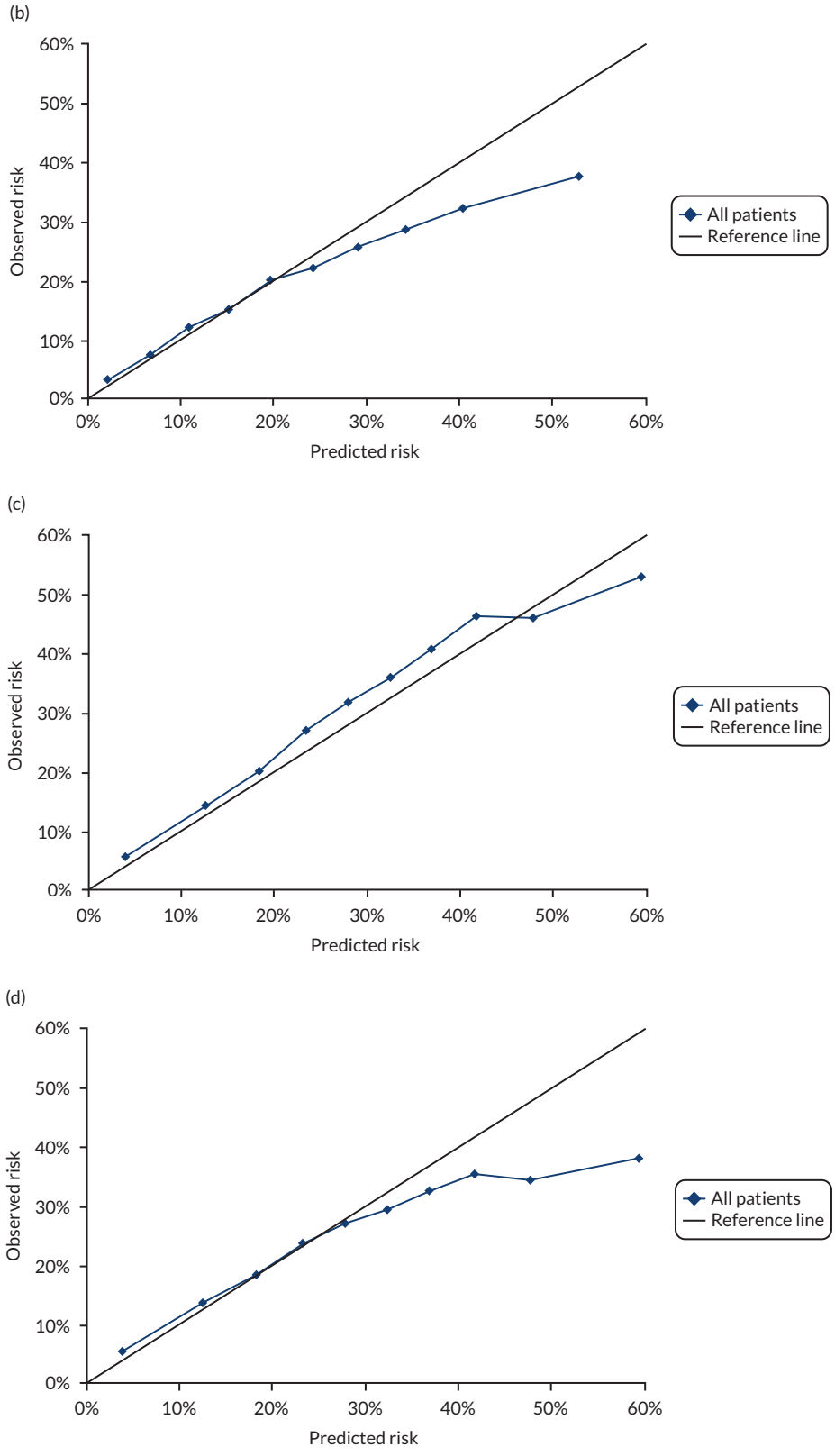

FIGURE 31 Calibration in CKD defined by Read code and eGFR. (a) Women with CKD defined by Read code or eGFR not accounting for competing risks;[a] (b) women with CKD defined by Read code or eGFR accounting for competing risks;[b] (c) men with CKD defined by Read code or eGFR not accounting for competing risks;[a] and (d) men with CKD defined by Read code or eGFR accounting for competing risks.[b] a, Observed risk is based on the Kaplan–Meier estimator, which does not account for competing mortality risk; and b, observed risk is based on the Aalen–Johansen estimator, which accounts for competing mortality risk.

Appendix 2 QRISK-Lifetime external validation

TABLE 31 Baseline data compared with QRISK-Lifetime derivation cohort

Data	Women external validation cohort (*N* = 1,260,329)	Men external validation cohort (*N* = 1,223,265)	All patients QRISK-Lifetime internal validation cohort (*N* = 1,267,159)
Age (years), mean (SD)	49.3 (14.2)	47.6 (13.0)	48.0 (14.2)
BMI (kg/m^2), mean (SD)	26.2 (5.8)	26.8 (4.6)	26.1 (4.5)
TC : HDL (mmol/l), mean (SD)	3.7 (1.1)	4.4 (1.3)	4.2 (1.3)
SBP (mmHg), mean (SD)	127 (18)	132 (16)	131.7 (20.5)
Ethnicity, *n* (%)			
White or not recorded	1,168,417 (92.7)	1,155,055 (94.4)	1,219,987 (96.3)
Indian	16,627 (1.3)	12,346 (1.0)	7577 (0.6)
Pakistani	6546 (0.5)	5031 (0.4)	3663 (0.3)
Bangladeshi	1649 (0.1)	1604 (0.1)	2632 (0.2)
Other Asian	10,118 (0.8)	7946 (0.6)	5032 (0.4)
Black Caribbean	8154 (0.6)	5913 (0.5)	4666 (0.4)
Black African	14,495 (1.2)	10,681 (0.9)	9471 (0.8)
Chinese	5135 (0.4)	2917 (0.2)	3068 (0.2)
Other	29,188 (2.3)	21,772 (1.8)	11,063 (0.8)
Smoking status, *n* (%)[a]			
Non-smoker	585,281 (59.3)	403,983 (48.4)	631,545 (49.8)
Former smoker	189,719 (19.2)	198,717 (23.8)	193,974 (15.3)
Light smoker	63,592 (6.4)	58,543 (7.0)	71,037 (5.6)
Moderate smoker	91,518 (9.3)	90,692 (10.9)	91,679 (7.2)
Heavy smoker	56,241 (5.7)	83,169 (10.0)	74,056 (5.8)
Family history of CHD in first-degree relative aged < 60 years, *n* (%)	88,164 (7.0)	68,814 (5.6)	143,593 (11.3)
Type 2 diabetes, *n* (%)	16,744 (1.3)	20,883 (1.7)	20,868 (1.7)
Treated hypertension, *n* (%)	115,548 (9.2)	82,387 (6.7)	67,986 (5.4)
Atrial fibrillation, *n* (%)	8164 (0.6)	10,528 (0.9)	6589 (0.5)
CKD, *n* (%)	6675 (0.5)	5403 (0.4)	1917 (0.2)
Rheumatoid arthritis, *n* (%)	12,357 (1.0)	4590 (0.4)	Not reported

CHD, coronary heart disease; SD, standard deviation.
a For this study, the percentage of non-missing data. For the QRISK-Lifetime derivation paper,[27] the percentage of all patients.
Source: Livingstone *et al.*[49]

Appendix 3 QFracture-2012 external validation codesets

TABLE 32 Read codes defining MOF, including hip fracture

Fracture type	CPRD Medcode	Read code	Read code description
Hip	2225	S30..00	Fracture of neck of femur
	1994	S30..11	Hip fracture
	38489	S300.00	Closed fracture proximal femur, transcervical
	39984	S300000	Cls # prox femur, intracapsular section, unspecified
	69919	S300100	Closed fracture proximal femur, transepiphyseal
	65690	S300200	Closed fracture proximal femur, midcervical section
	52194	S300300	Closed fracture proximal femur, basicervical
	51861	S300311	Closed fracture, base of neck of femur
	36391	S300400	Closed fracture head of femur
	17019	S300500	Cls # prox femur, subcapital, Garden grade unspec.
	34351	S300600	Closed fracture proximal femur, subcapital, Garden grade I
	33957	S300700	Closed fracture proximal femur, subcapital, Garden grade II
	36599	S300800	Closed fracture proximal femur, subcapital, Garden grade III
	34078	S300900	Closed fracture proximal femur, subcapital, Garden grade IV
	49209	S300y00	Closed fracture proximal femur, other transcervical
	68229	S300y11	Closed fracture of femur, subcapital
	62966	S300z00	Closed fracture proximal femur, transcervical, NOS
	5301	S302.00	Closed fracture of proximal femur, pertrochanteric
	19117	S302000	Cls # proximal femur, trochanteric section, unspecified
	19387	S302011	Closed fracture of femur, greater trochanter
	48337	S302012	Closed fracture of femur, lesser trochanter
	45141	S302100	Closed fracture proximal femur, intertrochanteric, two part
	29145	S302200	Closed fracture proximal femur, subtrochanteric
	51216	S302300	Cls # proximal femur, intertrochanteric, comminuted
	8648	S302400	Closed fracture of femur, intertrochanteric
	44735	S302z00	Cls # of proximal femur, pertrochanteric section, NOS
	28965	S304.00	Pertrochanteric fracture
	8243	S305.00	Subtrochanteric fracture
	24276	S30w.00	Closed fracture of unspecified proximal femur
	18273	S30y.00	Closed fracture of neck of femur NOS
	10570	S30y.11	Hip fracture NOS
	37662	S310000	Closed fracture of femur, unspecified part
	520	S31z.00	Fracture of femur, NOS

continued

TABLE 32 Read codes defining MOF, including hip fracture (*continued*)

Fracture type	CPRD Medcode	Read code	Read code description
Distal radius/ulna	5951	7K1LM00	Closed reduction of fracture of wrist
	18299	S234.00	Closed fracture of radius and ulna, lower end
	203	S234.11	Wrist fracture – closed
	18389	S234000	Closed fracture of forearm, lower end, unspecified
	343	S234100	Closed Colles' fracture
	52389	S234111	Smith's fracture – closed
	1742	S234200	Closed fracture of the distal radius, unspecified
	28708	S234600	Closed fracture radius and ulna, distal
	2862	S234700	Closed Smith's fracture
	40268	S234800	Closed Galeazzi fracture
	11066	S234900	Closed volar Barton's fracture
	53689	S234911	Closed volar Barton's fracture-dislocation
	65636	S234912	Closed volar Barton fracture-subluxation
	50053	S234A00	Closed dorsal Barton's fracture
	57736	S234A11	Closed dorsal Barton's fracture-dislocation
	107741	S234A12	Closed dorsal Barton fracture-subluxation
	44844	S234C00	Closed fracture distal radius, intra-articular, die-punch
	19058	S234D00	Closed fracture distal radius, extra-articular, other type
	28293	S234E00	Closed fracture distal radius, intra-articular, other type
	10033	S234F00	Closed Barton's fracture
	102302	S234G00	Greenstick fracture of distal radius
	27591	S234z00	Closed fracture of forearm, lower end, NOS
	199	S23B.00	Fracture of lower end of radius
	6213	S23C.00	Fracture of lower end of both ulna and radius
	50654	S23x000	Closed fracture of forearm, unspecified
	17952	S23x100	Closed fracture of radius (alone), unspecified
	137	S23x111	Fracture of radius NOS
	17922	S4C0000	Closed fracture-dislocation distal radio-ulnar joint
	38408	S4C0100	Closed fracture-dislocation radiocarpal joint
	44652	S4C2000	Closed fracture-subluxation, distal radio-ulnar joint
	50148	S4C2100	Closed fracture-subluxation radiocarpal joint
Proximal humerus	6379	7K1LF00	Closed reduction of fracture of humerus
	517	S22..00	Fracture of humerus
	11222	S220.00	Closed fracture of the proximal humerus
	44721	S220000	Closed fracture of proximal humerus, unspecified part
	11313	S220100	Closed fracture proximal humerus, neck
	33489	S220200	Closed fracture of proximal humerus, anatomical neck
	11044	S220300	Closed fracture proximal humerus, greater tuberosity
	28739	S220400	Closed fracture proximal humerus, head
	52406	S220500	Closed fracture of humerus, upper epiphysis
	40330	S220600	Closed fracture proximal humerus, three part

TABLE 32 Read codes defining MOF, including hip fracture (*continued*)

Fracture type	CPRD Medcode	Read code	Read code description
	29137	S220700	Closed fracture proximal humerus, four part
	38353	S220z00	Closed fracture of proximal humerus not otherwise specified
	19186	S222000	Closed fracture of humerus NOS
	2101	S226.00	Fracture of upper end of humerus
	10382	S22z.00	Fracture of humerus NOS
Vertebral	16895	N1y1.00	Fatigue fracture of vertebra
	44386	N331.14	Osteoporotic vertebral collapse
	15837	N331011	Collapse of thoracic vertebra
	17377	N331800	Osteoporosis + pathological fracture lumbar vertebrae
	12673	N331900	Osteoporosis + pathological fracture thoracic vertebrae
	48772	N331A00	Osteoporosis + pathological fracture cervical vertebrae
	9319	N331F00	Collapse of thoracic vertebra
	45736	N331H00	Collapse of cervical vertebra due to osteoporosis
	5841	N331J00	Collapse of lumbar vertebra due to osteoporosis
	19048	N331K00	Collapse of thoracic vertebra due to osteoporosis
	4013	N331L00	Collapse of vertebra due to osteoporosis NOS
	53337	S100H00	Closed fracture cervical vertebra, wedge
	27404	S102.00	Closed fracture thoracic vertebra
	28524	S102100	Closed fracture thoracic vertebra, wedge
	8266	S104100	Closed fracture lumbar vertebra, wedge
	5381	S15..00	Fracture of thoracic vertebra

NOS, not otherwise specified.

TABLE 33 *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision

Fracture type	ICD-10 code	ICD-10 code description
Hip	S72.0	Fracture of neck of femur
	S72.1	Pertrochanteric fracture
	S72.2	Subtrochanteric fracture
Distal radius/ulna	S52.5	Fracture of lower end of radius
	S52.6	Fracture of lower end of both ulna and radius
Proximal humerus	S42.2	Fracture of upper end of humerus
Vertebral	M48.5	Collapsed vertebra, not elsewhere classified
Osteoporotic	M80.0	Postmenopausal osteoporosis with pathological fracture
	M80.1	Postoophorectomy osteoporosis with pathological fracture
	M80.3	Postsurgical malabsorption osteoporosis with pathological fracture
	M80.5	Idiopathic osteoporosis with pathological fracture
	M80.8	Other osteoporosis with pathological fracture
	M80.9	Unspecified osteoporosis with pathological fracture

TABLE 34 Definitions of morbidity predictors for QFracture-2012 algorithm

Morbidity	Definition
Type 1 diabetes and type 2 diabetes	As defined for GP data in Kuan *et al.*[98]
Parental history of osteoporosis/hip fracture	Bespoke codeset (see *Table 35*)
Care home resident	Bespoke codeset (see *Table 35*)
Previous fracture	As per fracture outcomes (see *Table 32*) plus bespoke codeset for 'history of' codes (see *Table 35*)
History of falls	Bespoke codeset (see *Table 35*)
Dementia	As defined for GP data in Kuan *et al.*[98]
Cancer	As defined for GP data in Kuan *et al.*[98]
Asthma or COPD	As defined for GP data in Kuan *et al.*[98]
Heart attack, angina, stroke or TIA	CVD outcomes in GP data defined in supplementary file in Livingstone *et al.*[67]
Chronic liver disease	As defined for GP data in Kuan *et al.*[98]
CKD	As defined for GP data in Kuan *et al.*[98]
Parkinson's disease	As defined for GP data in Kuan *et al.*[98]
Rheumatoid arthritis or SLE	As defined for GP data in Kuan *et al.*[98]
Malabsorption[a]	Crohn's disease, ulcerative colitis and coeliac disease, as defined for GP data in Kuan *et al.*;[98] malabsorption, steatorrhoea or blind loop syndrome in bespoke codeset (see *Table 35*)
Endocrine problems[b]	Hyperparathyroidism as defined for GP data in Kuan *et al.*;[98] thyrotoxicosis and Cushing syndrome in bespoke codeset (see *Table 35*)
Epilepsy	As defined for GP data in Kuan *et al.*[98]

COPD, chronic obstructive pulmonary disease; SLE, systemic lupus erythematosus.
a Crohn's disease, ulcerative colitis, coeliac disease, steatorrhoea or blind loop syndrome.
b Thyrotoxicosis, hyperparathyroidism or Cushing syndrome.

TABLE 35 Read codes defining morbidity predictors (codesets created for this study)

Morbidity	CPRD Medcode	Read code	Read code description
Parenteral history of osteoporosis or hip fracture	11218	1268.00	FH: osteoporosis
Family history of osteoporosis or hip fracture	51427	12I6.00	FH: fragility fracture
	37204	12I4.00	FH: maternal hip fracture
	42319	12I5.00	FH: hip fracture in first-degree relative
	43219	12I8.00	FH: maternal hip fracture before age 75
Care home resident	13359	13F6100	Lives in a nursing home
	7653	9N1G.00	Seen in nursing home
	24956	13FK.00	Lives in a residential home
	13360	13F6.00	Nursing/other home
	49681	13FX.00	Lives in care home
	27968	13F7.00	Residential institution

TABLE 35 Read codes defining morbidity predictors (codesets created for this study) (*continued*)

Morbidity	CPRD Medcode	Read code	Read code description
	13361	13F4.11	Lives in warden-controlled accommodation
	30807	13F4000	Resident in sheltered accommodation
	98592	8Ce4.00	Preferred place of care – nursing home
	6859	9N1F.00	Seen in warden sup home
	93998	9b0i.00	Residential home visit note
	10993	ZLG4.00	Discharge to nursing home
	101003	9NFR.00	Home visit request by residential institution
	28773	ZV60700	[V]Sheltered housing
	100080	8Ce5.00	Preferred place of care – residential home
	7101	9N1F.12	Seen in old people's home
	59653	6991.00	Geriatric home admission exam
	73321	9b1P.00	Nursing home
	102493	8Ht..00	Admission to nursing home
	107443	9NFW000	Care home visit for initial patient assessment
	35187	9N1D.00	Seen in warden sup house
	35172	9N1E.00	Seen in warden sup flat
	34794	13F9.11	Living in sheltered accommodation
	21280	13F5200	Resident in part III accommodation
	107602	9NFW100	Care home visit for follow-up patient review
	42191	ZLG3.00	Discharge to residential home
	24828	Z177F00	Nursing home care
	73083	9b0Y.00	Nursing home visit note
	94070	8O24.00	Provision of continuing care in nursing home
	107757	9NFW.00	Care home visit
	59548	13FT.00	Lives in an old people's home
	102598	8Hs..00	Discharge to nursing home
	27936	8HE6.00	Delayed discharge to nursing home
	24816	Z177C00	Residential care
	50792	9N1F.11	Seen in Part 3 accommodation
	36096	13F5.11	Part 3 accommodation
	6991	9493.00	Patient died in nursing home
	43915	ZLG4100	Discharge to private nursing home
	49138	ZV63212	[V]Delayed discharge – nursing home vacancy awaited
	27360	13F5100	Part III accommodation arranged
	98758	13Zo.00	Previously lived in care home
	36905	ZLG5100	Discharge to warden-controlled accommodation

continued

TABLE 35 Read codes defining morbidity predictors (codesets created for this study) (*continued*)

Morbidity	CPRD Medcode	Read code	Read code description
	35040	ZLG5.00	Discharge to sheltered housing
	102230	M270100	Nursing home acquired pressure ulcer
	48549	ZLG3100	Discharge to private residential home
	95795	923O.00	FP22 – removal from residential institute
	67903	U105100	[X]Fall involving wheelchair occurrence residential instit'*n*
	46642	9b79.00	Other residential care homes managed by local authority
	66122	13F5111	Part 3 accommodation arranged
	99148	9b7A.00	Other residential care home man voluntary/private agents
	96836	ZK76.00	Temporary home care service provision
History of fracture[a]	17936	14G7.00	H/O: hip fracture
	18731	14G6.00	H/O: fragility fracture
	19235	14G8.00	H/O: vertebral fracture
History of falls	384	TC...11	Fall – accidental
	6815	TC...00	Accidental falls
	6008	16D..00	Falls
	4859	R200.12	[D] Geriatric fall
	6835	TCz..00	Accidental falls NOS
	8694	16D1.00	Recurrent falls
	8730	TCy..00	Other falls
	15112	TC5..00	Fall on same level from slipping, tripping or stumbling
	11307	TC0..00	Fall on or from stairs or steps
	11308	TCyz.00	Other accidental fall NOS
	17167	TC01.00	Fall on or from stairs
	11709	TC51.00	Fall on same level from tripping
	33887	TC4..00	Other fall from one level to another
	17728	TC01000	Fall on stairs
	108062	16D6.00	Fall
	18007	TC50.00	Fall on same level from slipping
	21081	TC01100	Fall from stairs
	26432	TC42100	Fall from bed
	7948	TC52.00	Fall on same level from stumbling
	33529	TC5z.00	Fall on same level from slipping
	98223	16D5.00	Fall onto outstretched hand
	41909	TC01z00	Fall on or from stairs NOS
	43092	TC02000	Fall on steps

TABLE 35 Read codes defining morbidity predictors (codesets created for this study) (*continued*)

Morbidity	CPRD Medcode	Read code	Read code description
	43571	TC3..00	Fall into hole or other opening in surface
	21306	TC4z.00	Fall from one level to another NOS
	53082	TC02100	Fall from steps
	44626	TC02.00	Fall on or from steps
	38818	TC42000	Fall from chair
	64696	TC0z.00	Fall on or from stairs or steps NOS
	7876	TC4yz00	Other fall from one level to another NOS
	41853	TC4y.00	Other fall from one level to another
	69020	TC4y200	Fall from stationary vehicle
	93574	8O9..00	Provision of telecare community alarm service
	53463	TC00.00	Fall on or from escalator
	56316	TC00000	Fall on escalator
	64722	TC02z00	Fall on or from steps NOS
	59404	TC42.00	Fall from chair or bed
	29568	TC3yz00	Fall into other hole
	55743	67ID.00	Falls advice – hip protectors advised
	48309	67IE.00	Falls advice – hip protectors supplied
	44119	8BIG.00	Falls caused by medication
	109088	9Nlf.00	Seen by community falls team
	16684	T04..00	Fall in
	58753	T040.00	Fall in train
	94933	T040100	Fall in train
	59911	T041.00	Fall on train
	97335	T04z.00	Fall in
	18097	T170.00	MVTA – fall down stairs of motor bus while board/alighting
	41114	T171.00	MVTA – fall from car in street while boarding/alighting
	60782	T53..00	Fall in
	110413	T53z.00	Fall in
	60003	TC42z00	Fall from chair or bed NOS
	17638	TH03.00	Late effects of accidental fall
	7970	U10..00	[X]Falls
	21903	U100.00	[X]Fall on same level involving ice and snow
	68559	U100000	[X]Fall on same level involving ice and snow occurrence home
	63515	U100200	[X]Fall sam lvl inv ice/snw occ sch oth inst/pub admin area

continued

TABLE 35 Read codes defining morbidity predictors (codesets created for this study) (*continued*)

Morbidity	CPRD Medcode	Read code	Read code description
	43615	U100300	[X]Fall same levl involv ice/snow
	60427	U100400	[X]Fall same levl inv ice and snow
	93148	U100500	[X]Fall same levl inv ice/snow
	71613	U100z00	[X]Fall same levl inv ice/snow
	29821	U101.00	[X]Fall on same level from slipping
	49035	U101000	[X]Fall same levl frm slip trip+stumb
	49210	U101100	[X]Fall same level from slip trip+stumb occ resid instit
	60424	U101200	[X]Fall sme levl slp trp+stmb occ sch
	49100	U101300	[X]Fall sme levl frm slip trip+stumb
	52452	U101400	[X]Fall same level from slip trip+stumb
	68616	U101500	[X]Fall sme lvl frm slip trip+stumb
	68895	U101600	[X]Fall same levl
	61705	U101700	[X]Fall same level from slip trip+stumbling
	49218	U101y00	[X]Fall same level
	68579	U101z00	[X]Fall same levl frm slip trip+stumbling
	111606	U102200	[X]Fall
	66934	U103000	[X]Oth fall same levl
	109428	U103500	[X]Oth fall sme levl coll/push anth pers occ trad/serv area
	62109	U103y00	[X]Oth fall sme levl coll/push anoth per occ oth spec place
	93454	U103z00	[X]Oth fall same levl coll/push anoth pers occ unspec place
	67230	U104.00	[X]Fall while being carried or supported by other persons
	52410	U104000	[X]Fall while carried/supported by other persons
	51851	U104100	[X]Fall whle carried/supported oth persons occ resid instit
	110968	U104z00	[X]Fall whle carr'd/supportd by oth per
	21349	U105.00	[X]Fall involving wheelchair
	98315	U105000	[X]Fall involving wheelchair
	67903	U105100	[X]Fall involving wheelchair occurrence residential instit'n
	85959	U105500	[X]Fall involving wheelchair occurrence at trade/service area
	98713	U105700	[X]Fall involving wheelchair
	109423	U105y00	[X]Fall involv wheelchair
	52374	U106.00	[X]Fall involving bed
	44419	U106000	[X]Fall involving bed

TABLE 35 Read codes defining morbidity predictors (codesets created for this study) (*continued*)

Morbidity	CPRD Medcode	Read code	Read code description
	69762	U106100	[X]Fall involving bed occurrence in residential institution
	50572	U107.00	[X]Fall involving chair
	68600	U107000	[X]Fall involving chair
	68617	U107z00	[X]Fall involving chair
	55553	U108.00	[X]Fall involving other furniture
	68591	U108000	[X]Fall involving other furniture
	66922	U108100	[X]Fall involv other furniture occurrn resident institut'n
	36402	U10A.00	[X]Fall on and from stairs and steps
	52432	U10A000	[X]Fall on and from stairs and steps
	52466	U10A100	[X]Fall on+from stair+step occurrence resident instit'n
	111571	U10A200	[X]Fall on+frm stair+step occ sch oth inst/pub adm area
	99385	U10A400	[X]Fall on+from stairs+steps occurrn on street/highway
	51284	U10A500	[X]Fall on+from stair+step occurrn at trade/servce area
	41105	U10A511	[X]Fall on or from escalator
	68613	U10Ay00	[X]Fall on+from stair+step occurrn at oth specif place
	64193	U10Az00	[X]Fall on+from stair+step occurrnce at unspecif place
	50316	U10D.00	[X]Fall from
	52380	U10D000	[X]Fall from out of/through building/structur occurn home
	100710	U10D100	[X]Fall from out of/thro buildng/struct occ resid instit'n
	110898	U10D400	[X]Fall from out/thro buildng/struct occ on street/highway
	92721	U10H.00	[X]Other fall from one level to another
	51669	U10H000	[X]Other fall from one level to another
	68609	U10H200	[X]Othr fall frm one level to anothr
	68562	U10H400	[X]Othr fall from one level to anothr occurrn street/h'way
	68604	U10H500	[X]Other fall frm one level to anothr occ at trde/serv area
	95961	U10H600	[X]Other fall frm one level to anoth occ indust/constr area
	72468	U10Hy00	[X]Other fall frm one levl to anothr occ at oth specif plce

continued

TABLE 35 Read codes defining morbidity predictors (codesets created for this study) (*continued*)

Morbidity	CPRD Medcode	Read code	Read code description
	49233	U10Hz00	[X]Othr fall frm one level to anothr occurrn at unspec plce
	48496	U10J.00	[X]Other fall on same level
	43191	U10J000	[X]Other fall on same level
	72474	U10J100	[X]Other fall on same level
	100060	U10J200	[X]Other fall on same levl occ schl oth inst/pub admin area
	101254	U10J400	[X]Other fall on same level
	68608	U10J600	[X]Other fall on same levl
	101523	U10Jy00	[X]Other fall on same level occurrn at oth specified place
	98876	U10Jz00	[X]Other fall on same level occurrence at unspecified place
	24776	U10z.00	[X]Unspecified fall
	10419	U10z000	[X]Unspecified fall
	46303	U10z100	[X]Unspecified fall
	55202	U10z300	[X]Unspecified fall
	97327	U10z400	[X]Unspecified fall
	106900	U10z700	[X]Unspecified fall
	96546	U10zy00	[X]Unspecified fall
	61170	U10zz00	[X]Unspecified fall
	6785	ZV71B00	[V]Examination and observation following a fall
Malabsorption[b]	9355	J69..00	Intestinal malabsorption
	5088	J69yz00	Other gastrointestinal tract malabsorption NOS
	4787	J690.15	Steatorrhea – idiopathic
	6663	J69y.00	Other intestinal malabsorption
	42715	J69z.00	Intestinal malabsorption NOS
	23498	J692.00	Blind loop syndrome
	31392	J69y600	Intestinal malabsorption of fat
	2482	D011100	Vit B12 defic anaemia due to malabsorption with proteinuria
	19441	C285.00	Adult osteomalacia due to malabsorption
	37440	J693.11	Postsurgical malabsorption – other
	49191	J69y200	Intestinal malabsorption of protein
	55481	D012300	Folate-deficiency anaemia due to malabsorption
	72529	Jyu9000	[X]Other intestinal malabsorption
	57647	J693100	Post gastrointestinal tract surgery malnutrition
	49739	J69y300	Intestinal malabsorption of carbohydrate
	93655	N330700	Postsurgical malabsorption osteoporosis

TABLE 35 Read codes defining morbidity predictors (codesets created for this study) (*continued*)

Morbidity	CPRD Medcode	Read code	Read code description
Endocrine problems[c]	1472	C02..11	Hyperthyroidism
	5257	C020.12	Graves' disease
	6245	1431.00	H/O: hyperthyroidism
	3857	C052.11	Autoimmune thyroiditis
	17604	C150.00	Cushing syndrome
	11947	L181500	Postpartum thyroiditis
	30799	C051.00	Subacute thyroiditis
	4898	C050.00	Acute thyroiditis
	18382	C150111	Drug-induced Cushing syndrome
	26362	212P.00	Hyperthyroidism resolved
	106640	C025.00	Subclinical hyperthyroidism
	21747	C051.11	De Quervain's thyroiditis
	20275	C150100	Iatrogenic Cushing syndrome
	60534	C150z00	Cushing syndrome NOS
	49508	C024.00	Thyrotoxicosis from ectopic thyroid nodule
	68626	FyuBD00	[X]Dysthyroid exophthalmos
	42323	C050z00	Acute thyroiditis NOS
	53682	C150200	Pituitary dependent Cushing syndrome
	65444	C05y.00	Other and unspecified chronic thyroiditis
	61026	C054.00	Iatrogenic thyroiditis
	53667	C053.11	Riedel's thyroiditis
	65907	C05y400	Chronic thyroiditis with transient thyrotoxicosis
	65754	C150500	Alcohol-induced pseudo-Cushing syndrome
	67972	C050000	Acute nonsuppurative thyroiditis
	65120	C150300	Ectopic ACTH secretion causing Cushing syndrome
	60690	F395100	Myopathy due to Cushing syndrome
	70967	C150000	Idiopathic Cushing syndrome
	56270	C024z00	Thyrotoxicosis from ectopic thyroid nodule NOS
	70773	C050100	Acute suppurative thyroiditis
	95807	Cyu4500	[X]Other Cushing syndrome
	64656	C024000	Thyrotoxicosis from ectopic thyroid nodule with no crisis

FH, family history; NOS, not otherwise specified.
a Used along with fracture outcomes to define baseline history of fracture.
b Malabsorption includes Crohn's disease, ulcerative colitis and coeliac disease, as defined by Kuan *et al.*[98] (these codes are for malabsorption, steatorrhoea or blind loop syndrome).
c Endocrine problems includes hyperparathyroidism, as defined by Kuan *et al.*[98] (these codes are for thyrotoxicosis and Cushing syndrome).

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
34916	Amitriptyline hydrochloride	Antidepressant
45242	Amitriptyline hydrochloride	Antidepressant
83	Amitriptyline hydrochloride	Antidepressant
33090	Amitriptyline hydrochloride	Antidepressant
52867	Amitriptyline hydrochloride	Antidepressant
24141	Amitriptyline hydrochloride	Antidepressant
57972	Amitriptyline hydrochloride	Antidepressant
55491	Amitriptyline hydrochloride	Antidepressant
70991	Amitriptyline hydrochloride	Antidepressant
61835	Amitriptyline hydrochloride	Antidepressant
76839	Amitriptyline hydrochloride	Antidepressant
45233	Amitriptyline hydrochloride	Antidepressant
34731	Amitriptyline hydrochloride	Antidepressant
66578	Amitriptyline hydrochloride	Antidepressant
80135	Amitriptyline hydrochloride	Antidepressant
57107	Amitriptyline hydrochloride	Antidepressant
65879	Amitriptyline hydrochloride	Antidepressant
24152	Amitriptyline hydrochloride	Antidepressant
59161	Amitriptyline hydrochloride	Antidepressant
34401	Amitriptyline hydrochloride	Antidepressant
46801	Amitriptyline hydrochloride	Antidepressant
64000	Amitriptyline hydrochloride	Antidepressant
79826	Amitriptyline hydrochloride	Antidepressant
70300	Amitriptyline hydrochloride	Antidepressant
76298	Amitriptyline hydrochloride	Antidepressant
46818	Amitriptyline hydrochloride	Antidepressant
76927	Amitriptyline hydrochloride	Antidepressant
487	Amitriptyline hydrochloride	Antidepressant
34197	Amitriptyline hydrochloride	Antidepressant
41729	Amitriptyline hydrochloride	Antidepressant
42394	Amitriptyline hydrochloride	Antidepressant
34474	Amitriptyline hydrochloride	Antidepressant
32439	Amitriptyline hydrochloride	Antidepressant
49	Amitriptyline hydrochloride	Antidepressant
34782	Amitriptyline hydrochloride	Antidepressant
54877	Amitriptyline hydrochloride	Antidepressant
24145	Amitriptyline hydrochloride	Antidepressant

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
55139	Amitriptyline hydrochloride	Antidepressant
42078	Amitriptyline hydrochloride	Antidepressant
71042	Amitriptyline hydrochloride	Antidepressant
65987	Amitriptyline hydrochloride	Antidepressant
64647	Amitriptyline hydrochloride	Antidepressant
79766	Amitriptyline hydrochloride	Antidepressant
34503	Amitriptyline hydrochloride	Antidepressant
24134	Amitriptyline hydrochloride	Antidepressant
66579	Amitriptyline hydrochloride	Antidepressant
60355	Amitriptyline hydrochloride	Antidepressant
77167	Amitriptyline hydrochloride	Antidepressant
65439	Amitriptyline hydrochloride	Antidepressant
66572	Amitriptyline hydrochloride	Antidepressant
24147	Amitriptyline hydrochloride	Antidepressant
34129	Amitriptyline hydrochloride	Antidepressant
6312	Amitriptyline hydrochloride	Antidepressant
78364	Amitriptyline hydrochloride	Antidepressant
67127	Amitriptyline hydrochloride	Antidepressant
34224	Amitriptyline hydrochloride	Antidepressant
60410	Amitriptyline hydrochloride	Antidepressant
4682	Amitriptyline hydrochloride	Antidepressant
40396	Amitriptyline hydrochloride	Antidepressant
1888	Amitriptyline hydrochloride	Antidepressant
34274	Amitriptyline hydrochloride	Antidepressant
34634	Amitriptyline hydrochloride	Antidepressant
64330	Amitriptyline hydrochloride	Antidepressant
78221	Amitriptyline hydrochloride	Antidepressant
46970	Amitriptyline hydrochloride	Antidepressant
34182	Amitriptyline hydrochloride	Antidepressant
69712	Amitriptyline hydrochloride	Antidepressant
33624	Amitriptyline hydrochloride	Antidepressant
34107	Amitriptyline hydrochloride	Antidepressant
4690	Amitriptyline hydrochloride	Antidepressant
34251	Amitriptyline hydrochloride	Antidepressant
59820	Amitriptyline hydrochloride	Antidepressant
64141	Amitriptyline hydrochloride	Antidepressant

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
76952	Amitriptyline hydrochloride	Antidepressant
77497	Amitriptyline hydrochloride	Antidepressant
26213	Amitriptyline hydrochloride	Antidepressant
20026	Amitriptyline hydrochloride	Antidepressant
27008	Amitriptyline hydrochloride	Antidepressant
24680	Amitriptyline hydrochloride	Antidepressant
2486	Amitriptyline hydrochloride	Antidepressant
2985	Amitriptyline hydrochloride	Antidepressant
8726	Amitriptyline hydrochloride	Antidepressant
7751	Amitriptyline hydrochloride	Antidepressant
8332	Amitriptyline hydrochloride	Antidepressant
19779	Amitriptyline hydrochloride	Antidepressant
182	Amitriptyline hydrochloride	Antidepressant
22070	Amitriptyline hydrochloride	Antidepressant
3777	Amitriptyline hydrochloride	Antidepressant
2525	Amitriptyline hydrochloride	Antidepressant
48065	Amitriptyline hydrochloride	Antidepressant
8878	Amitriptyline hydrochloride	Antidepressant
8831	Amitriptyline hydrochloride	Antidepressant
21081	Amitriptyline hydrochloride/chlordiazepoxide	Antidepressant
18342	Amitriptyline hydrochloride/chlordiazepoxide	Antidepressant
11963	Amitriptyline hydrochloride/chlordiazepoxide	Antidepressant
14534	Amitriptyline hydrochloride/chlordiazepoxide	Antidepressant
3490	Amitriptyline hydrochloride/perphenazine	Antidepressant
595	Amitriptyline hydrochloride/perphenazine	Antidepressant
1453	Amitriptyline hydrochloride/perphenazine	Antidepressant
1208	Amitriptyline hydrochloride/perphenazine	Antidepressant
38827	Amitriptyline hydrochloride/perphenazine	Antidepressant
16323	Amitriptyline hydrochloride/perphenazine	Antidepressant
6894	Amitriptyline hydrochloride/perphenazine	Antidepressant
3652	Amoxapine	Antidepressant
4411	Amoxapine	Antidepressant
17319	Amoxapine	Antidepressant
3351	Amoxapine	Antidepressant
21357	Amoxapine	Antidepressant
24723	Amoxapine	Antidepressant
15380	Amoxapine	Antidepressant

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
14398	Amoxapine	Antidepressant
55289	Amoxapine	Antidepressant
12227	Butriptyline hydrochloride	Antidepressant
32457	Butriptyline hydrochloride	Antidepressant
18932	Butriptyline hydrochloride	Antidepressant
3195	Clomipramine	Antidepressant
30375	Clomipramine hydrochloride	Antidepressant
26513	Clomipramine hydrochloride	Antidepressant
7515	Clomipramine hydrochloride	Antidepressant
3657	Clomipramine hydrochloride	Antidepressant
8719	Clomipramine hydrochloride	Antidepressant
7693	Clomipramine hydrochloride	Antidepressant
7894	Clomipramine hydrochloride	Antidepressant
3194	Clomipramine hydrochloride	Antidepressant
34866	Clomipramine hydrochloride	Antidepressant
68665	Clomipramine hydrochloride	Antidepressant
41628	Clomipramine hydrochloride	Antidepressant
62620	Clomipramine hydrochloride	Antidepressant
43561	Clomipramine hydrochloride	Antidepressant
3670	Clomipramine hydrochloride	Antidepressant
34245	Clomipramine hydrochloride	Antidepressant
41563	Clomipramine hydrochloride	Antidepressant
45350	Clomipramine hydrochloride	Antidepressant
65762	Clomipramine hydrochloride	Antidepressant
8720	Clomipramine hydrochloride	Antidepressant
64458	Clomipramine hydrochloride	Antidepressant
3925	Clomipramine hydrochloride	Antidepressant
45318	Clomipramine hydrochloride	Antidepressant
41597	Clomipramine hydrochloride	Antidepressant
53187	Clomipramine hydrochloride	Antidepressant
78324	Clomipramine hydrochloride	Antidepressant
65804	Clomipramine hydrochloride	Antidepressant
53161	Clomipramine hydrochloride	Antidepressant
38274	Clomipramine hydrochloride	Antidepressant
78057	Clomipramine hydrochloride	Antidepressant
8661	Clomipramine hydrochloride	Antidepressant

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
7981	Desipramine	Antidepressant
7979	Desipramine	Antidepressant
43024	Dosulepin hydrochloride	Antidepressant
77130	Dosulepin hydrochloride	Antidepressant
70838	Dosulepin hydrochloride	Antidepressant
84	Dosulepin hydrochloride	Antidepressant
23426	Dosulepin hydrochloride	Antidepressant
34745	Dosulepin hydrochloride	Antidepressant
34643	Dosulepin hydrochloride	Antidepressant
31824	Dosulepin hydrochloride	Antidepressant
44853	Dosulepin hydrochloride	Antidepressant
29875	Dosulepin hydrochloride	Antidepressant
33164	Dosulepin hydrochloride	Antidepressant
34641	Dosulepin hydrochloride	Antidepressant
76317	Dosulepin hydrochloride	Antidepressant
34223	Dosulepin hydrochloride	Antidepressant
50722	Dosulepin hydrochloride	Antidepressant
71023	Dosulepin hydrochloride	Antidepressant
70593	Dosulepin hydrochloride	Antidepressant
74	Dosulepin hydrochloride	Antidepressant
32121	Dosulepin hydrochloride	Antidepressant
19186	Dosulepin hydrochloride	Antidepressant
67728	Dosulepin hydrochloride	Antidepressant
42734	Dosulepin hydrochloride	Antidepressant
31826	Dosulepin hydrochloride	Antidepressant
34525	Dosulepin hydrochloride	Antidepressant
62681	Dosulepin hydrochloride	Antidepressant
71059	Dosulepin hydrochloride	Antidepressant
34058	Dosulepin hydrochloride	Antidepressant
57926	Dosulepin hydrochloride	Antidepressant
1940	Dosulepin hydrochloride	Antidepressant
15632	Dosulepin hydrochloride	Antidepressant
21820	Dosulepin hydrochloride	Antidepressant
21819	Dosulepin hydrochloride	Antidepressant
67990	Dosulepin hydrochloride	Antidepressant
51758	Dosulepin hydrochloride	Antidepressant
1169	Dosulepin hydrochloride	Antidepressant

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
2320	Dosulepin hydrochloride	Antidepressant
30376	Dosulepin hydrochloride	Antidepressant
21157	Dosulepin hydrochloride	Antidepressant
19168	Dosulepin hydrochloride	Antidepressant
45737	Dosulepin hydrochloride	Antidepressant
6054	Dosulepin hydrochloride	Antidepressant
10948	Dosulepin hydrochloride	Antidepressant
5190	Doxepin hydrochloride	Antidepressant
9558	Doxepin hydrochloride	Antidepressant
15975	Doxepin hydrochloride	Antidepressant
3842	Doxepin hydrochloride	Antidepressant
3554	Doxepin hydrochloride	Antidepressant
5073	Doxepin hydrochloride	Antidepressant
73363	Doxepin hydrochloride	Antidepressant
7059	Doxepin hydrochloride	Antidepressant
35258	Doxepin hydrochloride	Antidepressant
35493	Doxepin hydrochloride	Antidepressant
10413	Doxepin hydrochloride	Antidepressant
12129	Doxepin hydrochloride	Antidepressant
12125	Doxepin hydrochloride	Antidepressant
14519	Doxepin hydrochloride	Antidepressant
40777	Doxepin Hydrochloride	Antidepressant
2936	Fluphenazine hydrochloride/nortriptyline hydrochloride	Antidepressant
7780	Fluphenazine hydrochloride/nortriptyline hydrochloride	Antidepressant
1310	Imipramine hydrochloride	Antidepressant
41681	Imipramine hydrochloride	Antidepressant
34222	Imipramine hydrochloride	Antidepressant
67935	Imipramine hydrochloride	Antidepressant
71253	Imipramine hydrochloride	Antidepressant
70287	Imipramine hydrochloride	Antidepressant
32863	Imipramine hydrochloride	Antidepressant
34872	Imipramine hydrochloride	Antidepressant
1809	Imipramine hydrochloride	Antidepressant
34813	Imipramine hydrochloride	Antidepressant
34355	Imipramine hydrochloride	Antidepressant
41408	Imipramine hydrochloride	Antidepressant

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
8055	Imipramine hydrochloride	Antidepressant
42247	Imipramine hydrochloride	Antidepressant
33074	Imipramine hydrochloride	Antidepressant
2579	Imipramine hydrochloride	Antidepressant
56501	Imipramine hydrochloride	Antidepressant
7910	Imipramine hydrochloride	Antidepressant
4404	Imipramine hydrochloride	Antidepressant
27476	Iprindole	Antidepressant
27733	Iprindole	Antidepressant
24700	Iprindole	Antidepressant
31672	Iprindole	Antidepressant
79397	Lofepramine	Antidepressant
58450	Lofepramine hydrochloride	Antidepressant
2093	Lofepramine hydrochloride	Antidepressant
41627	Lofepramine hydrochloride	Antidepressant
114	Lofepramine hydrochloride	Antidepressant
34046	Lofepramine hydrochloride	Antidepressant
34950	Lofepramine hydrochloride	Antidepressant
71067	Lofepramine hydrochloride	Antidepressant
74586	Lofepramine hydrochloride	Antidepressant
66100	Lofepramine hydrochloride	Antidepressant
34578	Lofepramine hydrochloride	Antidepressant
68657	Lofepramine hydrochloride	Antidepressant
67742	Lofepramine hydrochloride	Antidepressant
56703	Lofepramine hydrochloride	Antidepressant
34672	Lofepramine hydrochloride	Antidepressant
60591	Lofepramine hydrochloride	Antidepressant
56229	Lofepramine hydrochloride	Antidepressant
43534	Lofepramine hydrochloride	Antidepressant
4218	Lofepramine hydrochloride	Antidepressant
77717	Lofepramine hydrochloride	Antidepressant
25444	Lofepramine hydrochloride	Antidepressant
7468	Mianserin hydrochloride	Antidepressant
8144	Mianserin hydrochloride	Antidepressant
8585	Mianserin hydrochloride	Antidepressant
3083	Mianserin hydrochloride	Antidepressant
47363	Mianserin hydrochloride	Antidepressant

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
4329	Mianserin hydrochloride	Antidepressant
6255	Mianserin hydrochloride	Antidepressant
12368	Mianserin hydrochloride	Antidepressant
11956	Mianserin hydrochloride	Antidepressant
12192	Mianserin hydrochloride	Antidepressant
7677	Nortriptyline hydrochloride	Antidepressant
8640	Nortriptyline hydrochloride	Antidepressant
3183	Nortriptyline hydrochloride	Antidepressant
65237	Nortriptyline hydrochloride	Antidepressant
55970	Nortriptyline hydrochloride	Antidepressant
72626	Nortriptyline hydrochloride	Antidepressant
68228	Nortriptyline hydrochloride	Antidepressant
3903	Nortriptyline hydrochloride	Antidepressant
48216	Nortriptyline hydrochloride	Antidepressant
63276	Nortriptyline hydrochloride	Antidepressant
66201	Nortriptyline hydrochloride	Antidepressant
78224	Nortriptyline hydrochloride	Antidepressant
69317	Nortriptyline hydrochloride	Antidepressant
17183	Nortriptyline hydrochloride	Antidepressant
12549	Nortriptyline hydrochloride	Antidepressant
12353	Nortriptyline hydrochloride	Antidepressant
4118	Nortriptyline hydrochloride	Antidepressant
39145	Nortriptyline hydrochloride	Antidepressant
7678	Nortriptyline hydrochloride	Antidepressant
8493	Nortriptyline hydrochloride/fluphenazine hydrochloride	Antidepressant
14578	Nortriptyline hydrochloride/fluphenazine hydrochloride	Antidepressant
20571	Nortriptyline hydrochloride/fluphenazine hydrochloride	Antidepressant
60929	Protriptyline hydrochloride	Antidepressant
7755	Protriptyline hydrochloride	Antidepressant
7816	Protriptyline hydrochloride	Antidepressant
11187	Protriptyline hydrochloride	Antidepressant
7756	Protriptyline hydrochloride	Antidepressant
4194	Trazodone hydrochloride	Antidepressant
4003	Trazodone hydrochloride	Antidepressant
4874	Trazodone hydrochloride	Antidepressant
8174	Trazodone hydrochloride	Antidepressant

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
13621	Trazodone hydrochloride	Antidepressant
1730	Trazodone hydrochloride	Antidepressant
34580	Trazodone hydrochloride	Antidepressant
73639	Trazodone hydrochloride	Antidepressant
19181	Trazodone hydrochloride	Antidepressant
41709	Trazodone hydrochloride	Antidepressant
41710	Trazodone hydrochloride	Antidepressant
65152	Trazodone hydrochloride	Antidepressant
72291	Trazodone hydrochloride	Antidepressant
66749	Trazodone hydrochloride	Antidepressant
12710	Trazodone hydrochloride	Antidepressant
4020	Trazodone hydrochloride	Antidepressant
73419	Trazodone hydrochloride	Antidepressant
77915	Trazodone hydrochloride	Antidepressant
73636	Trazodone hydrochloride	Antidepressant
76480	Trazodone hydrochloride	Antidepressant
30983	Trazodone hydrochloride	Antidepressant
29857	Trazodone hydrochloride	Antidepressant
34470	Trazodone hydrochloride	Antidepressant
55137	Trazodone hydrochloride	Antidepressant
55138	Trazodone hydrochloride	Antidepressant
57226	Trazodone hydrochloride	Antidepressant
3355	Trazodone hydrochloride	Antidepressant
34003	Trazodone hydrochloride	Antidepressant
71031	Trazodone hydrochloride	Antidepressant
29339	Trazodone hydrochloride	Antidepressant
41609	Trazodone hydrochloride	Antidepressant
34421	Trazodone hydrochloride	Antidepressant
61842	Trazodone hydrochloride	Antidepressant
6442	Trazodone hydrochloride	Antidepressant
59931	Trazodone hydrochloride	Antidepressant
70521	Trazodone hydrochloride	Antidepressant
77474	Trazodone hydrochloride	Antidepressant
61657	Trazodone hydrochloride	Antidepressant
69355	Trazodone hydrochloride	Antidepressant
8928	Trimipramine maleate	Antidepressant
2532	Trimipramine maleate	Antidepressant

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
2531	Trimipramine maleate	Antidepressant
4310	Trimipramine maleate	Antidepressant
42228	Trimipramine maleate	Antidepressant
53808	Trimipramine maleate	Antidepressant
2039	Trimipramine maleate	Antidepressant
45226	Trimipramine maleate	Antidepressant
57978	Trimipramine maleate	Antidepressant
66493	Trimipramine maleate	Antidepressant
3196	Trimipramine maleate	Antidepressant
65445	Trimipramine maleate	Antidepressant
66919	Trimipramine maleate	Antidepressant
65213	Trimipramine maleate	Antidepressant
12309	Viloxazine hydrochloride	Antidepressant
12111	Viloxazine hydrochloride	Antidepressant
3861	Citalopram hydrobromide	Antidepressant
79784	Citalopram hydrobromide	Antidepressant
63953	Citalopram hydrobromide	Antidepressant
1712	Citalopram hydrobromide	Antidepressant
2408	Citalopram hydrobromide	Antidepressant
34498	Citalopram hydrobromide	Antidepressant
476	Citalopram hydrobromide	Antidepressant
34586	Citalopram hydrobromide	Antidepressant
64423	Citalopram hydrobromide	Antidepressant
32848	Citalopram hydrobromide	Antidepressant
49165	Citalopram hydrobromide	Antidepressant
42660	Citalopram hydrobromide	Antidepressant
52100	Citalopram hydrobromide	Antidepressant
59650	Citalopram hydrobromide	Antidepressant
53787	Citalopram hydrobromide	Antidepressant
71005	Citalopram hydrobromide	Antidepressant
33720	Citalopram hydrobromide	Antidepressant
52408	Citalopram hydrobromide	Antidepressant
34436	Citalopram hydrobromide	Antidepressant
45286	Citalopram hydrobromide	Antidepressant
75697	Citalopram hydrobromide	Antidepressant
52824	Citalopram hydrobromide	Antidepressant

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
59193	Citalopram hydrobromide	Antidepressant
63441	Citalopram hydrobromide	Antidepressant
34499	Citalopram hydrobromide	Antidepressant
60888	Citalopram hydrobromide	Antidepressant
41528	Citalopram hydrobromide	Antidepressant
56355	Citalopram hydrobromide	Antidepressant
34413	Citalopram hydrobromide	Antidepressant
54827	Citalopram hydrobromide	Antidepressant
34722	Citalopram hydrobromide	Antidepressant
67	Citalopram hydrobromide	Antidepressant
34356	Citalopram hydrobromide	Antidepressant
67097	Citalopram hydrobromide	Antidepressant
34871	Citalopram hydrobromide	Antidepressant
53394	Citalopram hydrobromide	Antidepressant
48026	Citalopram hydrobromide	Antidepressant
56009	Citalopram hydrobromide	Antidepressant
58476	Citalopram hydrobromide	Antidepressant
52607	Citalopram hydrobromide	Antidepressant
52354	Citalopram hydrobromide	Antidepressant
34415	Citalopram hydrobromide	Antidepressant
34970	Citalopram hydrobromide	Antidepressant
73417	Citalopram hydrobromide	Antidepressant
72373	Citalopram hydrobromide	Antidepressant
26016	Citalopram hydrobromide	Antidepressant
34966	Citalopram hydrobromide	Antidepressant
60568	Citalopram hydrobromide	Antidepressant
34822	Citalopram hydrobromide	Antidepressant
71848	Citalopram hydrobromide	Antidepressant
43519	Citalopram hydrobromide	Antidepressant
4770	Citalopram hydrobromide	Antidepressant
36746	Citalopram hydrobromide	Antidepressant
69571	Citalopram hydrobromide	Antidepressant
46977	Citalopram hydrobromide	Antidepressant
75075	Citalopram hydrobromide	Antidepressant
60839	Citalopram hydrobromide	Antidepressant
70790	Citalopram hydrobromide	Antidepressant
55033	Citalopram hydrobromide	Antidepressant

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
75702	Citalopram hydrobromide	Antidepressant
34603	Citalopram hydrobromide	Antidepressant
45223	Citalopram hydrobromide	Antidepressant
34466	Citalopram hydrobromide	Antidepressant
45304	Citalopram hydrobromide	Antidepressant
46926	Citalopram hydrobromide	Antidepressant
32546	Citalopram hydrobromide	Antidepressant
29756	Citalopram hydrobromide	Antidepressant
74753	Citalopram hydrobromide	Antidepressant
815	Citalopram hydrochloride	Antidepressant
513	Citalopram hydrochloride	Antidepressant
57936	Citalopram hydrochloride	Antidepressant
56292	Citalopram hydrochloride	Antidepressant
72124	Citalopram hydrochloride	Antidepressant
74785	Escitalopram oxalate	Antidepressant
648	Escitalopram oxalate	Antidepressant
74858	Escitalopram oxalate	Antidepressant
26056	Escitalopram oxalate	Antidepressant
6360	Escitalopram oxalate	Antidepressant
41062	Escitalopram oxalate	Antidepressant
785	Escitalopram oxalate	Antidepressant
603	Escitalopram oxalate	Antidepressant
63916	Escitalopram oxalate	Antidepressant
74993	Escitalopram oxalate	Antidepressant
20152	Escitalopram oxalate	Antidepressant
6218	Escitalopram oxalate	Antidepressant
72773	Escitalopram oxalate	Antidepressant
40726	Escitalopram oxalate	Antidepressant
6405	Escitalopram oxalate	Antidepressant
33071	Fluoxetine hydrochloride	Antidepressant
67431	Fluoxetine hydrochloride	Antidepressant
69941	Fluoxetine hydrochloride	Antidepressant
77881	Fluoxetine hydrochloride	Antidepressant
42499	Fluoxetine hydrochloride	Antidepressant
75645	Fluoxetine hydrochloride	Antidepressant
38890	Fluoxetine hydrochloride	Antidepressant

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
22	Fluoxetine hydrochloride	Antidepressant
19183	Fluoxetine hydrochloride	Antidepressant
71852	Fluoxetine hydrochloride	Antidepressant
45329	Fluoxetine hydrochloride	Antidepressant
60962	Fluoxetine hydrochloride	Antidepressant
75799	Fluoxetine hydrochloride	Antidepressant
67736	Fluoxetine hydrochloride	Antidepressant
45247	Fluoxetine hydrochloride	Antidepressant
75688	Fluoxetine hydrochloride	Antidepressant
34202	Fluoxetine hydrochloride	Antidepressant
34294	Fluoxetine hydrochloride	Antidepressant
69525	Fluoxetine hydrochloride	Antidepressant
59358	Fluoxetine hydrochloride	Antidepressant
66744	Fluoxetine hydrochloride	Antidepressant
34288	Fluoxetine hydrochloride	Antidepressant
42107	Fluoxetine hydrochloride	Antidepressant
62155	Fluoxetine hydrochloride	Antidepressant
19470	Fluoxetine hydrochloride	Antidepressant
45224	Fluoxetine hydrochloride	Antidepressant
67769	Fluoxetine hydrochloride	Antidepressant
34456	Fluoxetine hydrochloride	Antidepressant
34849	Fluoxetine hydrochloride	Antidepressant
67092	Fluoxetine hydrochloride	Antidepressant
45316	Fluoxetine hydrochloride	Antidepressant
33410	Fluoxetine hydrochloride	Antidepressant
60534	Fluoxetine hydrochloride	Antidepressant
60138	Fluoxetine hydrochloride	Antidepressant
2548	Fluoxetine hydrochloride	Antidepressant
34216	Fluoxetine hydrochloride	Antidepressant
42803	Fluoxetine hydrochloride	Antidepressant
60619	Fluoxetine hydrochloride	Antidepressant
73414	Fluoxetine hydrochloride	Antidepressant
30258	Fluoxetine hydrochloride	Antidepressant
36893	Fluoxetine hydrochloride	Antidepressant
68266	Fluoxetine hydrochloride	Antidepressant
69685	Fluoxetine hydrochloride	Antidepressant
74886	Fluoxetine hydrochloride	Antidepressant

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
67496	Fluoxetine hydrochloride	Antidepressant
79590	Fluoxetine hydrochloride	Antidepressant
67562	Fluoxetine hydrochloride	Antidepressant
75068	Fluoxetine hydrochloride	Antidepressant
78889	Fluoxetine hydrochloride	Antidepressant
4075	Fluoxetine hydrochloride	Antidepressant
75247	Fluoxetine hydrochloride	Antidepressant
67888	Fluoxetine hydrochloride	Antidepressant
34856	Fluoxetine hydrochloride	Antidepressant
62335	Fluoxetine hydrochloride	Antidepressant
14740	Fluoxetine hydrochloride	Antidepressant
67758	Fluoxetine hydrochloride	Antidepressant
77381	Fluoxetine hydrochloride	Antidepressant
418	Fluoxetine hydrochloride	Antidepressant
48220	Fluoxetine hydrochloride	Antidepressant
61335	Fluoxetine hydrochloride	Antidepressant
69542	Fluoxetine hydrochloride	Antidepressant
57532	Fluoxetine hydrochloride	Antidepressant
252	Fluoxetine hydrochloride	Antidepressant
75943	Fluoxetine hydrochloride	Antidepressant
4907	Fluoxetine hydrochloride	Antidepressant
37256	Fluoxetine hydrochloride	Antidepressant
33779	Fluoxetine hydrochloride	Antidepressant
29786	Fluoxetine hydrochloride	Antidepressant
12123	Fluvoxamine maleate	Antidepressant
2897	Fluvoxamine maleate	Antidepressant
2290	Fluvoxamine maleate	Antidepressant
48045	Fluvoxamine maleate	Antidepressant
44861	Fluvoxamine maleate	Antidepressant
43518	Fluvoxamine maleate	Antidepressant
2880	Fluvoxamine maleate	Antidepressant
3391	Nefazodone hydrochloride	Antidepressant
4297	Nefazodone hydrochloride	Antidepressant
63827	Nefazodone hydrochloride	Antidepressant
4554	Nefazodone hydrochloride	Antidepressant
4011	Nefazodone hydrochloride	Antidepressant

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
67757	Nefazodone hydrochloride	Antidepressant
35021	Paroxetine hydrochloride	Antidepressant
76946	Paroxetine hydrochloride	Antidepressant
59288	Paroxetine hydrochloride	Antidepressant
67259	Paroxetine hydrochloride	Antidepressant
527	Paroxetine hydrochloride	Antidepressant
50	Paroxetine hydrochloride	Antidepressant
34419	Paroxetine hydrochloride	Antidepressant
32899	Paroxetine hydrochloride	Antidepressant
73668	Paroxetine hydrochloride	Antidepressant
40892	Paroxetine hydrochloride	Antidepressant
34351	Paroxetine hydrochloride	Antidepressant
55023	Paroxetine hydrochloride	Antidepressant
33978	Paroxetine hydrochloride	Antidepressant
1397	Paroxetine hydrochloride	Antidepressant
34587	Paroxetine hydrochloride	Antidepressant
40165	Paroxetine hydrochloride	Antidepressant
64785	Paroxetine hydrochloride	Antidepressant
78843	Paroxetine hydrochloride	Antidepressant
68325	Paroxetine hydrochloride	Antidepressant
35112	Paroxetine hydrochloride	Antidepressant
66292	Paroxetine hydrochloride	Antidepressant
74588	Paroxetine hydrochloride	Antidepressant
841	Paroxetine hydrochloride	Antidepressant
73589	Paroxetine hydrochloride	Antidepressant
77650	Paroxetine hydrochloride	Antidepressant
3601	Paroxetine hydrochloride	Antidepressant
1575	Paroxetine hydrochloride	Antidepressant
55537	Paroxetine hydrochloride	Antidepressant
76772	Paroxetine hydrochloride	Antidepressant
79383	Paroxetine hydrochloride	Antidepressant
79381	Paroxetine hydrochloride	Antidepressant
75054	Paroxetine hydrochloride	Antidepressant
65771	Sertraline	Antidepressant
4352	Sertraline hydrochloride	Antidepressant
77385	Sertraline hydrochloride	Antidepressant
1612	Sertraline hydrochloride	Antidepressant

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
727	Sertraline hydrochloride	Antidepressant
55146	Sertraline hydrochloride	Antidepressant
62950	Sertraline hydrochloride	Antidepressant
61503	Sertraline hydrochloride	Antidepressant
59600	Sertraline hydrochloride	Antidepressant
62692	Sertraline hydrochloride	Antidepressant
69726	Sertraline hydrochloride	Antidepressant
67928	Sertraline hydrochloride	Antidepressant
66560	Sertraline hydrochloride	Antidepressant
54933	Sertraline hydrochloride	Antidepressant
66413	Sertraline hydrochloride	Antidepressant
68756	Sertraline hydrochloride	Antidepressant
44944	Sertraline hydrochloride	Antidepressant
73962	Sertraline hydrochloride	Antidepressant
49519	Sertraline hydrochloride	Antidepressant
77607	Sertraline hydrochloride	Antidepressant
78278	Sertraline hydrochloride	Antidepressant
62819	Sertraline hydrochloride	Antidepressant
54826	Sertraline hydrochloride	Antidepressant
78626	Sertraline hydrochloride	Antidepressant
73759	Sertraline hydrochloride	Antidepressant
54081	Sertraline hydrochloride	Antidepressant
488	Sertraline hydrochloride	Antidepressant
32401	Sertraline hydrochloride	Antidepressant
58723	Sertraline hydrochloride	Antidepressant
42387	Sertraline hydrochloride	Antidepressant
45915	Sertraline hydrochloride	Antidepressant
62693	Sertraline hydrochloride	Antidepressant
69725	Sertraline hydrochloride	Antidepressant
63481	Sertraline hydrochloride	Antidepressant
58664	Sertraline hydrochloride	Antidepressant
67730	Sertraline hydrochloride	Antidepressant
69898	Sertraline hydrochloride	Antidepressant
55488	Sertraline hydrochloride	Antidepressant
75952	Sertraline hydrochloride	Antidepressant
62927	Sertraline hydrochloride	Antidepressant

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
75405	Sertraline hydrochloride	Antidepressant
7328	Sertraline hydrochloride	Antidepressant
77538	Sertraline hydrochloride	Antidepressant
77707	Sertraline hydrochloride	Antidepressant
40494	Agomelatine	Antidepressant
40295	Agomelatine	Antidepressant
74774	Duloxetine hydrochloride	Antidepressant
7122	Duloxetine hydrochloride	Antidepressant
13151	Duloxetine hydrochloride	Antidepressant
62688	Duloxetine hydrochloride	Antidepressant
63370	Duloxetine hydrochloride	Antidepressant
65618	Duloxetine hydrochloride	Antidepressant
65809	Duloxetine hydrochloride	Antidepressant
66412	Duloxetine hydrochloride	Antidepressant
70405	Duloxetine hydrochloride	Antidepressant
70728	Duloxetine hydrochloride	Antidepressant
73298	Duloxetine hydrochloride	Antidepressant
74907	Duloxetine hydrochloride	Antidepressant
79628	Duloxetine hydrochloride	Antidepressant
6895	Duloxetine hydrochloride	Antidepressant
14849	Duloxetine hydrochloride	Antidepressant
51383	Duloxetine hydrochloride	Antidepressant
63216	Duloxetine hydrochloride	Antidepressant
63763	Duloxetine hydrochloride	Antidepressant
64442	Duloxetine hydrochloride	Antidepressant
65888	Duloxetine hydrochloride	Antidepressant
65892	Duloxetine hydrochloride	Antidepressant
66405	Duloxetine hydrochloride	Antidepressant
68096	Duloxetine hydrochloride	Antidepressant
69428	Duloxetine hydrochloride	Antidepressant
69752	Duloxetine hydrochloride	Antidepressant
69965	Duloxetine hydrochloride	Antidepressant
72211	Duloxetine hydrochloride	Antidepressant
73540	Duloxetine hydrochloride	Antidepressant
73868	Duloxetine hydrochloride	Antidepressant
74190	Duloxetine hydrochloride	Antidepressant
78777	Duloxetine hydrochloride	Antidepressant

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
76857	Duloxetine hydrochloride	Antidepressant
6421	Mirtazapine	Antidepressant
43253	Mirtazapine	Antidepressant
64101	Mirtazapine	Antidepressant
43241	Mirtazapine	Antidepressant
66580	Mirtazapine	Antidepressant
61856	Mirtazapine	Antidepressant
43248	Mirtazapine	Antidepressant
43246	Mirtazapine	Antidepressant
68680	Mirtazapine	Antidepressant
55482	Mirtazapine	Antidepressant
58291	Mirtazapine	Antidepressant
77865	Mirtazapine	Antidepressant
65555	Mirtazapine	Antidepressant
43237	Mirtazapine	Antidepressant
48698	Mirtazapine	Antidepressant
54012	Mirtazapine	Antidepressant
6795	Mirtazapine	Antidepressant
43239	Mirtazapine	Antidepressant
53699	Mirtazapine	Antidepressant
66183	Mirtazapine	Antidepressant
59953	Mirtazapine	Antidepressant
46668	Mirtazapine	Antidepressant
66752	Mirtazapine	Antidepressant
43242	Mirtazapine	Antidepressant
54342	Mirtazapine	Antidepressant
54644	Mirtazapine	Antidepressant
74557	Mirtazapine	Antidepressant
43257	Mirtazapine	Antidepressant
16154	Mirtazapine	Antidepressant
53321	Mirtazapine	Antidepressant
61547	Mirtazapine	Antidepressant
47966	Mirtazapine	Antidepressant
68544	Mirtazapine	Antidepressant
6488	Mirtazapine	Antidepressant
43250	Mirtazapine	Antidepressant

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
53648	Mirtazapine	Antidepressant
48185	Mirtazapine	Antidepressant
68052	Mirtazapine	Antidepressant
69420	Mirtazapine	Antidepressant
76187	Mirtazapine	Antidepressant
59694	Mirtazapine	Antidepressant
742	Mirtazapine	Antidepressant
47945	Mirtazapine	Antidepressant
40160	Mirtazapine	Antidepressant
54792	Mirtazapine	Antidepressant
69005	Mirtazapine	Antidepressant
77488	Mirtazapine	Antidepressant
78654	Mirtazapine	Antidepressant
60538	Mirtazapine	Antidepressant
56209	Mirtazapine	Antidepressant
68933	Mirtazapine	Antidepressant
71543	Mirtazapine	Antidepressant
63403	Mirtazapine	Antidepressant
6481	Mirtazapine	Antidepressant
43235	Mirtazapine	Antidepressant
43236	Mirtazapine	Antidepressant
43256	Mirtazapine	Antidepressant
43247	Mirtazapine	Antidepressant
64139	Mirtazapine	Antidepressant
43234	Mirtazapine	Antidepressant
49820	Mirtazapine	Antidepressant
6854	Mirtazapine	Antidepressant
33337	Mirtazapine	Antidepressant
58625	Mirtazapine	Antidepressant
59954	Mirtazapine	Antidepressant
64223	Mirtazapine	Antidepressant
77377	Mirtazapine	Antidepressant
4726	Mirtazapine	Antidepressant
67272	Mirtazapine	Antidepressant
60370	Mirtazapine	Antidepressant
6846	Mirtazapine	Antidepressant
50892	Mirtazapine	Antidepressant

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
10083	Mirtazapine	Antidepressant
53543	Mirtazapine	Antidepressant
15268	Mirtazapine	Antidepressant
9534	Nefazodone hydrochloride	Antidepressant
15163	Reboxetine mesilate	Antidepressant
2356	Reboxetine mesilate	Antidepressant
54747	Tryptophan	Antidepressant
5611	Tryptophan	Antidepressant
20504	Tryptophan	Antidepressant
12221	Tryptophan	Antidepressant
54686	Tryptophan	Antidepressant
4422	Tryptophan	Antidepressant
52516	Venlafaxine hydrochloride	Antidepressant
52074	Venlafaxine hydrochloride	Antidepressant
71806	Venlafaxine hydrochloride	Antidepressant
61236	Venlafaxine hydrochloride	Antidepressant
45664	Venlafaxine hydrochloride	Antidepressant
45959	Venlafaxine hydrochloride	Antidepressant
65738	Venlafaxine hydrochloride	Antidepressant
67271	Venlafaxine hydrochloride	Antidepressant
623	Venlafaxine hydrochloride	Antidepressant
6274	Venlafaxine hydrochloride	Antidepressant
67288	Venlafaxine hydrochloride	Antidepressant
77089	Venlafaxine hydrochloride	Antidepressant
9182	Venlafaxine hydrochloride	Antidepressant
74010	Venlafaxine hydrochloride	Antidepressant
5710	Venlafaxine hydrochloride	Antidepressant
51280	Venlafaxine hydrochloride	Antidepressant
65899	Venlafaxine hydrochloride	Antidepressant
74011	Venlafaxine hydrochloride	Antidepressant
75894	Venlafaxine hydrochloride	Antidepressant
1474	Venlafaxine hydrochloride	Antidepressant
76771	Venlafaxine hydrochloride	Antidepressant
43968	Venlafaxine hydrochloride	Antidepressant
43673	Venlafaxine hydrochloride	Antidepressant
41299	Venlafaxine hydrochloride	Antidepressant

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
48199	Venlafaxine hydrochloride	Antidepressant
41314	Venlafaxine hydrochloride	Antidepressant
41033	Venlafaxine hydrochloride	Antidepressant
59753	Venlafaxine hydrochloride	Antidepressant
60843	Venlafaxine hydrochloride	Antidepressant
40817	Venlafaxine hydrochloride	Antidepressant
40815	Venlafaxine hydrochloride	Antidepressant
39809	Venlafaxine hydrochloride	Antidepressant
39770	Venlafaxine hydrochloride	Antidepressant
57751	Venlafaxine hydrochloride	Antidepressant
52716	Venlafaxine hydrochloride	Antidepressant
40514	Venlafaxine hydrochloride	Antidepressant
40515	Venlafaxine hydrochloride	Antidepressant
70420	Venlafaxine hydrochloride	Antidepressant
70495	Venlafaxine hydrochloride	Antidepressant
69819	Venlafaxine hydrochloride	Antidepressant
70315	Venlafaxine hydrochloride	Antidepressant
50081	Venlafaxine hydrochloride	Antidepressant
59035	Venlafaxine hydrochloride	Antidepressant
49511	Venlafaxine hydrochloride	Antidepressant
58726	Venlafaxine hydrochloride	Antidepressant
74516	Venlafaxine hydrochloride	Antidepressant
58681	Venlafaxine hydrochloride	Antidepressant
55501	Venlafaxine hydrochloride	Antidepressant
2654	Venlafaxine hydrochloride	Antidepressant
70806	Venlafaxine hydrochloride	Antidepressant
60549	Venlafaxine hydrochloride	Antidepressant
71782	Venlafaxine hydrochloride	Antidepressant
43334	Venlafaxine hydrochloride	Antidepressant
39360	Venlafaxine hydrochloride	Antidepressant
50934	Venlafaxine hydrochloride	Antidepressant
62734	Venlafaxine hydrochloride	Antidepressant
65666	Venlafaxine hydrochloride	Antidepressant
40054	Venlafaxine hydrochloride	Antidepressant
58837	Venlafaxine hydrochloride	Antidepressant
45806	Venlafaxine hydrochloride	Antidepressant
301	Venlafaxine hydrochloride	Antidepressant

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
56662	Venlafaxine hydrochloride	Antidepressant
73667	Venlafaxine hydrochloride	Antidepressant
68050	Venlafaxine hydrochloride	Antidepressant
75525	Venlafaxine hydrochloride	Antidepressant
59923	Venlafaxine hydrochloride	Antidepressant
70353	Venlafaxine hydrochloride	Antidepressant
51361	Venlafaxine hydrochloride	Antidepressant
60895	Venlafaxine hydrochloride	Antidepressant
51699	Venlafaxine hydrochloride	Antidepressant
13237	Venlafaxine hydrochloride	Antidepressant
2617	Venlafaxine hydrochloride	Antidepressant
470	Venlafaxine hydrochloride	Antidepressant
71257	Venlafaxine hydrochloride	Antidepressant
59563	Venlafaxine hydrochloride	Antidepressant
68876	Venlafaxine hydrochloride	Antidepressant
43203	Venlafaxine hydrochloride	Antidepressant
39359	Venlafaxine hydrochloride	Antidepressant
1222	Venlafaxine hydrochloride	Antidepressant
60449	Venlafaxine hydrochloride	Antidepressant
73658	Venlafaxine hydrochloride	Antidepressant
66437	Venlafaxine hydrochloride	Antidepressant
56457	Venlafaxine hydrochloride	Antidepressant
63859	Venlafaxine hydrochloride	Antidepressant
53326	Venlafaxine hydrochloride	Antidepressant
63268	Venlafaxine hydrochloride	Antidepressant
40062	Venlafaxine hydrochloride	Antidepressant
40407	Venlafaxine hydrochloride	Antidepressant
45818	Venlafaxine hydrochloride	Antidepressant
40059	Venlafaxine hydrochloride	Antidepressant
44936	Venlafaxine hydrochloride	Antidepressant
44937	Venlafaxine hydrochloride	Antidepressant
71932	Venlafaxine hydrochloride	Antidepressant
70931	Venlafaxine hydrochloride	Antidepressant
40092	Venlafaxine hydrochloride	Antidepressant
67563	Venlafaxine hydrochloride	Antidepressant
40277	Venlafaxine hydrochloride	Antidepressant

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
76727	Venlafaxine hydrochloride	Antidepressant
75263	Venlafaxine hydrochloride	Antidepressant
40517	Venlafaxine hydrochloride	Antidepressant
42600	Venlafaxine hydrochloride	Antidepressant
40764	Venlafaxine hydrochloride	Antidepressant
40917	Venlafaxine hydrochloride	Antidepressant
40049	Venlafaxine hydrochloride	Antidepressant
78585	Venlafaxine hydrochloride	Antidepressant
40048	Venlafaxine hydrochloride	Antidepressant
75848	Venlafaxine hydrochloride	Antidepressant
55424	Venlafaxine hydrochloride	Antidepressant
67874	Vortioxetine hydrobromide	Antidepressant
69991	Vortioxetine hydrobromide	Antidepressant
69992	Vortioxetine hydrobromide	Antidepressant
65483	Vortioxetine hydrobromide	Antidepressant
66890	Vortioxetine hydrobromide	Antidepressant
65482	Vortioxetine hydrobromide	Antidepressant
25945	Iproniazide	Antidepressant
18290	Iproniazide	Antidepressant
41731	Isocarboxazid	Antidepressant
12207	Isocarboxazid	Antidepressant
12503	Isocarboxazid	Antidepressant
9206	Moclobemide	Antidepressant
5832	Moclobemide	Antidepressant
2883	Moclobemide	Antidepressant
67305	Moclobemide	Antidepressant
41747	Moclobemide	Antidepressant
5187	Moclobemide	Antidepressant
3349	Phenelzine sulfate	Antidepressant
4321	Phenelzine sulfate	Antidepressant
10787	Tranylcypromine sulfate	Antidepressant
3783	Tranylcypromine sulfate	Antidepressant
41654	Tranylcypromine sulfate	Antidepressant
3356	Trifluoperazine hydrochloride/tranylcypromine sulphate	Antidepressant
3955	Trifluoperazine hydrochloride/tranylcypromine sulphate	Antidepressant
24890	Trifluoperazine hydrochloride/tranylcypromine sulphate	Antidepressant
28215	Dexamethasone sodium phosphate	Corticosteroid

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
37500	Dexamethasone sodium phosphate	Corticosteroid
14906	Dexamethasone sodium phosphate	Corticosteroid
61316	Dexamethasone sodium phosphate	Corticosteroid
53173	Dexamethasone sodium phosphate	Corticosteroid
19259	Dexamethasone sodium phosphate	Corticosteroid
47598	Dexamethasone sodium phosphate	Corticosteroid
61958	Dexamethasone sodium phosphate	Corticosteroid
56940	Dexamethasone sodium phosphate	Corticosteroid
35453	Dexamethasone sodium phosphate	Corticosteroid
10657	Dexamethasone sodium phosphate	Corticosteroid
13972	Dexamethasone sodium phosphate	Corticosteroid
26299	Dexamethasone sodium phosphate	Corticosteroid
13952	Dexamethasone sodium phosphate	Corticosteroid
26454	Dexamethasone sodium phosphate	Corticosteroid
31948	Dexamethasone sodium phosphate	Corticosteroid
34083	Dexamethasone sodium phosphate	Corticosteroid
4233	Dexamethasone sodium phosphate	Corticosteroid
8108	Hydrocortisone acetate	Corticosteroid
1893	Hydrocortisone acetate	Corticosteroid
925	Lidocaine hydrochloride/methylprednisolone acetate	Corticosteroid
48800	Methylprednisolone acetate	Corticosteroid
48748	Methylprednisolone acetate	Corticosteroid
48746	Methylprednisolone acetate	Corticosteroid
14982	Methylprednisolone acetate	Corticosteroid
71106	Methylprednisolone acetate	Corticosteroid
27413	Methylprednisolone acetate	Corticosteroid
33132	Methylprednisolone acetate	Corticosteroid
35349	Methylprednisolone acetate	Corticosteroid
35040	Methylprednisolone acetate	Corticosteroid
35688	Methylprednisolone acetate	Corticosteroid
1133	Methylprednisolone acetate	Corticosteroid
5493	Methylprednisolone acetate	Corticosteroid
20157	Methylprednisolone acetate/lidocaine hydrochloride	Corticosteroid
50253	Methylprednisolone acetate/lidocaine hydrochloride	Corticosteroid
49076	Methylprednisolone acetate/lidocaine hydrochloride	Corticosteroid
50734	Methylprednisolone acetate/lidocaine hydrochloride	Corticosteroid

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
7405	Methylprednisolone acetate/lidocaine hydrochloride	Corticosteroid
35156	Methylprednisolone acetate/lidocaine hydrochloride	Corticosteroid
18266	Methylprednisolone sodium succinate	Corticosteroid
13397	Methylprednisolone sodium succinate	Corticosteroid
12405	Methylprednisolone sodium succinate	Corticosteroid
18765	Methylprednisolone sodium succinate	Corticosteroid
14188	Methylprednisolone sodium succinate	Corticosteroid
25226	Methylprednisolone sodium succinate	Corticosteroid
25839	Methylprednisolone sodium succinate	Corticosteroid
23511	Methylprednisolone sodium succinate	Corticosteroid
21540	Methylprednisolone sodium succinate	Corticosteroid
14962	Triamcinolone acetonide	Corticosteroid
35578	Triamcinolone acetonide	Corticosteroid
14335	Triamcinolone acetonide	Corticosteroid
14958	Triamcinolone acetonide	Corticosteroid
50216	Triamcinolone acetonide	Corticosteroid
22047	Triamcinolone acetonide	Corticosteroid
50026	Triamcinolone acetonide	Corticosteroid
33131	Triamcinolone acetonide	Corticosteroid
16583	Triamcinolone acetonide	Corticosteroid
48406	Triamcinolone acetonide	Corticosteroid
9368	Triamcinolone acetonide	Corticosteroid
11123	Triamcinolone acetonide	Corticosteroid
4488	Triamcinolone acetonide	Corticosteroid
30244	Triamcinolone acetonide	Corticosteroid
4125	Triamcinolone acetonide	Corticosteroid
4123	Triamcinolone acetonide	Corticosteroid
8864	Triamcinolone acetonide	Corticosteroid
13981	Triamcinolone acetonide	Corticosteroid
768	Triamcinolone acetonide	Corticosteroid
37737	Triamcinolone acetonide	Corticosteroid
3703	Triamcinolone acetonide	Corticosteroid
16582	Triamcinolone acetonide	Corticosteroid
50854	Triamcinolone hexacetonide	Corticosteroid
50853	Triamcinolone hexacetonide	Corticosteroid
57856	Triamcinolone hexacetonide	Corticosteroid
66867	Triamcinolone hexacetonide	Corticosteroid

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
15016	Triamcinolone hexacetonide	Corticosteroid
7992	Triamcinolone hexacetonide	Corticosteroid
10864	Betamethasone	Corticosteroid
11149	Betamethasone	Corticosteroid
7286	Betamethasone sodium phosphate	Corticosteroid
64235	Betamethasone sodium phosphate	Corticosteroid
68306	Betamethasone sodium phosphate	Corticosteroid
1971	Betamethasone sodium phosphate	Corticosteroid
50225	Betamethasone sodium phosphate	Corticosteroid
12398	Cortisone acetate	Corticosteroid
229	Cortisone acetate	Corticosteroid
53143	Cortisone acetate	Corticosteroid
7548	Cortisone acetate	Corticosteroid
53705	Cortisone acetate	Corticosteroid
18637	Cortisone acetate	Corticosteroid
12400	Cortisone acetate	Corticosteroid
10574	Cortisone acetate	Corticosteroid
23210	Cortisone acetate	Corticosteroid
22555	Deflazacort	Corticosteroid
29112	Deflazacort	Corticosteroid
20577	Deflazacort	Corticosteroid
41335	Deflazacort	Corticosteroid
9375	Deflazacort	Corticosteroid
78839	Deflazacort	Corticosteroid
17410	Deflazacort	Corticosteroid
3992	Deflazacort	Corticosteroid
53207	Dexamethasone	Corticosteroid
9994	Dexamethasone	Corticosteroid
34801	Dexamethasone	Corticosteroid
71926	Dexamethasone	Corticosteroid
78335	Dexamethasone	Corticosteroid
45234	Dexamethasone	Corticosteroid
66724	Dexamethasone	Corticosteroid
56443	Dexamethasone	Corticosteroid
76339	Dexamethasone	Corticosteroid
77085	Dexamethasone	Corticosteroid

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
52396	Dexamethasone	Corticosteroid
77849	Dexamethasone	Corticosteroid
74156	Dexamethasone	Corticosteroid
74157	Dexamethasone	Corticosteroid
36055	Dexamethasone	Corticosteroid
1280	Dexamethasone	Corticosteroid
62909	Dexamethasone	Corticosteroid
60120	Dexamethasone	Corticosteroid
34880	Dexamethasone	Corticosteroid
68182	Dexamethasone	Corticosteroid
64747	Dexamethasone	Corticosteroid
5157	Dexamethasone	Corticosteroid
54793	Dexamethasone	Corticosteroid
70611	Dexamethasone	Corticosteroid
78214	Dexamethasone	Corticosteroid
70893	Dexamethasone	Corticosteroid
68489	Dexamethasone	Corticosteroid
72537	Dexamethasone	Corticosteroid
69572	Dexamethasone	Corticosteroid
4779	Dexamethasone	Corticosteroid
55401	Dexamethasone	Corticosteroid
34915	Dexamethasone	Corticosteroid
186	Dexamethasone	Corticosteroid
74436	Dexamethasone	Corticosteroid
56347	Dexamethasone	Corticosteroid
68593	Dexamethasone	Corticosteroid
73216	Dexamethasone	Corticosteroid
21903	Dexamethasone	Corticosteroid
60064	Dexamethasone sodium phosphate	Corticosteroid
64766	Dexamethasone sodium phosphate	Corticosteroid
66200	Dexamethasone sodium phosphate	Corticosteroid
68103	Dexamethasone sodium phosphate	Corticosteroid
4943	Dexamethasone sodium phosphate	Corticosteroid
58474	Dexamethasone sodium phosphate	Corticosteroid
71404	Dexamethasone sodium phosphate	Corticosteroid
77483	Dexamethasone sodium phosphate	Corticosteroid
66524	Dexamethasone sodium phosphate	Corticosteroid

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
66287	Dexamethasone sodium phosphate	Corticosteroid
68860	Dexamethasone sodium phosphate	Corticosteroid
21218	Dexamethasone sodium phosphate	Corticosteroid
72848	Dexamethasone sodium phosphate	Corticosteroid
79684	Dexamethasone sodium phosphate	Corticosteroid
64050	Dexamethasone sodium phosphate	Corticosteroid
78307	Dexamethasone sodium phosphate	Corticosteroid
21668	Dexamethasone sodium phosphate	Corticosteroid
26300	Dexamethasone sodium phosphate	Corticosteroid
11334	Dexamethasone sodium phosphate	Corticosteroid
75064	Hydrocortisone	Corticosteroid
74502	Hydrocortisone	Corticosteroid
75065	Hydrocortisone	Corticosteroid
76671	Hydrocortisone	Corticosteroid
3418	Hydrocortisone	Corticosteroid
65984	Hydrocortisone	Corticosteroid
64787	Hydrocortisone	Corticosteroid
66666	Hydrocortisone	Corticosteroid
38022	Hydrocortisone	Corticosteroid
75019	Hydrocortisone	Corticosteroid
51849	Hydrocortisone	Corticosteroid
51872	Hydrocortisone	Corticosteroid
64059	Hydrocortisone	Corticosteroid
54794	Hydrocortisone	Corticosteroid
4535	Hydrocortisone	Corticosteroid
66327	Hydrocortisone	Corticosteroid
57931	Hydrocortisone	Corticosteroid
75384	Hydrocortisone	Corticosteroid
77646	Hydrocortisone	Corticosteroid
51871	Hydrocortisone	Corticosteroid
75937	Hydrocortisone	Corticosteroid
52053	Hydrocortisone	Corticosteroid
75020	Hydrocortisone	Corticosteroid
53953	Hydrocortisone	Corticosteroid
63138	Hydrocortisone	Corticosteroid
14076	Hydrocortisone	Corticosteroid

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
51722	Hydrocortisone	Corticosteroid
51824	Hydrocortisone	Corticosteroid
75729	Hydrocortisone	Corticosteroid
74497	Hydrocortisone	Corticosteroid
71620	Hydrocortisone	Corticosteroid
38054	Hydrocortisone	Corticosteroid
10754	Hydrocortisone	Corticosteroid
6098	Hydrocortisone	Corticosteroid
13043	Hydrocortisone	Corticosteroid
77994	Hydrocortisone	Corticosteroid
58592	Hydrocortisone	Corticosteroid
59418	Hydrocortisone	Corticosteroid
35172	Hydrocortisone sodium phosphate	Corticosteroid
35175	Hydrocortisone sodium phosphate	Corticosteroid
71905	Hydrocortisone sodium phosphate	Corticosteroid
37638	Hydrocortisone sodium phosphate	Corticosteroid
43355	Hydrocortisone sodium phosphate	Corticosteroid
77821	Hydrocortisone sodium phosphate	Corticosteroid
9574	Hydrocortisone sodium phosphate	Corticosteroid
2615	Hydrocortisone sodium phosphate	Corticosteroid
49707	Hydrocortisone sodium succinate	Corticosteroid
49498	Hydrocortisone sodium succinate	Corticosteroid
51167	Hydrocortisone sodium succinate	Corticosteroid
54715	Hydrocortisone sodium succinate	Corticosteroid
34166	Hydrocortisone sodium succinate	Corticosteroid
13350	Hydrocortisone sodium succinate	Corticosteroid
3754	Hydrocortisone sodium succinate	Corticosteroid
3651	Hydrocortisone sodium succinate	Corticosteroid
18042	Methylprednisolone	Corticosteroid
8261	Methylprednisolone	Corticosteroid
10683	Methylprednisolone	Corticosteroid
15555	Methylprednisolone	Corticosteroid
14172	Methylprednisolone	Corticosteroid
10552	Methylprednisolone	Corticosteroid
76923	Methylprednisolone	Corticosteroid
10684	Methylprednisolone	Corticosteroid
2130	Methylprednisolone	Corticosteroid

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
78546	Prednisolone	Corticosteroid
27962	Prednisolone	Corticosteroid
28859	Prednisolone	Corticosteroid
25272	Prednisolone	Corticosteroid
23512	Prednisolone	Corticosteroid
20095	Prednisolone	Corticosteroid
34914	Prednisolone	Corticosteroid
5913	Prednisolone	Corticosteroid
5490	Prednisolone	Corticosteroid
59283	Prednisolone	Corticosteroid
34631	Prednisolone	Corticosteroid
66645	Prednisolone	Corticosteroid
66015	Prednisolone	Corticosteroid
80110	Prednisolone	Corticosteroid
59229	Prednisolone	Corticosteroid
69568	Prednisolone	Corticosteroid
78129	Prednisolone	Corticosteroid
64007	Prednisolone	Corticosteroid
64008	Prednisolone	Corticosteroid
64009	Prednisolone	Corticosteroid
69686	Prednisolone	Corticosteroid
64128	Prednisolone	Corticosteroid
63172	Prednisolone	Corticosteroid
58234	Prednisolone	Corticosteroid
65626	Prednisolone	Corticosteroid
34109	Prednisolone	Corticosteroid
9727	Prednisolone	Corticosteroid
33691	Prednisolone	Corticosteroid
64416	Prednisolone	Corticosteroid
74239	Prednisolone	Corticosteroid
66914	Prednisolone	Corticosteroid
72421	Prednisolone	Corticosteroid
80050	Prednisolone	Corticosteroid
578	Prednisolone	Corticosteroid
34452	Prednisolone	Corticosteroid
34404	Prednisolone	Corticosteroid

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
73553	Prednisolone	Corticosteroid
58384	Prednisolone	Corticosteroid
63549	Prednisolone	Corticosteroid
28376	Prednisolone	Corticosteroid
2368	Prednisolone	Corticosteroid
38407	Prednisolone	Corticosteroid
61132	Prednisolone	Corticosteroid
75001	Prednisolone	Corticosteroid
34660	Prednisolone	Corticosteroid
51753	Prednisolone	Corticosteroid
34748	Prednisolone	Corticosteroid
56891	Prednisolone	Corticosteroid
34978	Prednisolone	Corticosteroid
59338	Prednisolone	Corticosteroid
557	Prednisolone	Corticosteroid
28375	Prednisolone	Corticosteroid
34461	Prednisolone	Corticosteroid
76020	Prednisolone	Corticosteroid
55480	Prednisolone	Corticosteroid
79930	Prednisolone	Corticosteroid
68497	Prednisolone	Corticosteroid
63066	Prednisolone	Corticosteroid
73294	Prednisolone	Corticosteroid
54434	Prednisolone	Corticosteroid
63082	Prednisolone	Corticosteroid
67076	Prednisolone	Corticosteroid
53313	Prednisolone	Corticosteroid
2704	Prednisolone	Corticosteroid
53336	Prednisolone	Corticosteroid
78144	Prednisolone	Corticosteroid
41745	Prednisolone	Corticosteroid
65020	Prednisolone	Corticosteroid
54118	Prednisolone	Corticosteroid
67507	Prednisolone	Corticosteroid
69811	Prednisolone	Corticosteroid
44	Prednisolone	Corticosteroid
31532	Prednisolone	Corticosteroid

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
32803	Prednisolone	Corticosteroid
66550	Prednisolone	Corticosteroid
67107	Prednisolone	Corticosteroid
73678	Prednisolone	Corticosteroid
58987	Prednisolone	Corticosteroid
34393	Prednisolone	Corticosteroid
59912	Prednisolone	Corticosteroid
45302	Prednisolone	Corticosteroid
75763	Prednisolone	Corticosteroid
33988	Prednisolone	Corticosteroid
33990	Prednisolone	Corticosteroid
95	Prednisolone	Corticosteroid
21417	Prednisolone	Corticosteroid
29333	Prednisolone	Corticosteroid
58000	Prednisolone	Corticosteroid
58369	Prednisolone	Corticosteroid
34781	Prednisolone	Corticosteroid
60421	Prednisolone	Corticosteroid
41515	Prednisolone	Corticosteroid
55024	Prednisolone	Corticosteroid
63791	Prednisolone	Corticosteroid
67559	Prednisolone	Corticosteroid
61162	Prednisolone	Corticosteroid
32835	Prednisolone	Corticosteroid
64221	Prednisolone	Corticosteroid
1063	Prednisolone sodium phosphate	Corticosteroid
47142	Prednisolone sodium phosphate	Corticosteroid
955	Prednisolone sodium phosphate	Corticosteroid
61689	Prednisolone sodium phosphate	Corticosteroid
74493	Prednisolone sodium phosphate	Corticosteroid
63214	Prednisolone sodium phosphate	Corticosteroid
19141	Prednisolone sodium phosphate	Corticosteroid
78789	Prednisolone sodium phosphate	Corticosteroid
70603	Prednisolone sodium phosphate	Corticosteroid
77760	Prednisolone sodium phosphate	Corticosteroid
24224	Prednisolone sodium phosphate	Corticosteroid

continued

TABLE 36 Clinical Practice Research Datalink Prodcodes defining prescribing variables (corticosteroids are all oral or injectable preparations) (*continued*)

CPRD Prodcode	CPRD drug/substance (drug name as recorded in CPRD)	QFracture-2012 variable
31327	Prednisolone steaglate	Corticosteroid
3345	Prednisolone steaglate	Corticosteroid
21833	Prednisone	Corticosteroid
54432	Prednisone	Corticosteroid
44803	Prednisone	Corticosteroid
44802	Prednisone	Corticosteroid
44380	Prednisone	Corticosteroid
3557	Prednisone	Corticosteroid
46711	Prednisone	Corticosteroid
58061	Prednisone	Corticosteroid
44723	Prednisone	Corticosteroid
62656	Prednisone	Corticosteroid
43544	Prednisone	Corticosteroid
2949	Prednisone	Corticosteroid
24014	Triamcinolone acetonide	Corticosteroid
15617	Triamcinolone acetonide	Corticosteroid
19908	Triamcinolone acetonide	Corticosteroid
23111	Triamcinolone acetonide	Corticosteroid

Appendix 4 QFracture-2012 external validation, and CFracture derivation and internal validation

TABLE 37 Missing data in the fracture data set

Missing data	How missingness was handled in analysis	External validation cohort		All patients original QFracture-2012 internal validation cohort (*N* = 1,583,373), *n* (%) missing data
		Women, *n* (%) missing da	Men, *n* (%) missing data	
Age	Never missing	0	0	0
Sex	Never missing	0	0	0
Socioeconomic status	Excluded from cohort	0	0	0
BMI	Imputed	932,720 (34.0)	1,233,196 (45.9)	418,478 (26.4)
Smoking status	Imputed	780,226 (28.4)	963,580 (35.9)	258,144 (16.3)
Alcohol status	Imputed	698,902 (25.4)	866,622 (32.3)	461,740 (29.2)
Ethnicity	Assumed to be white	1,278,931 (46.6)	1,494,450 (55.7)	855,485 (54.0)
Conditions and prescribing variables	Assumed to be absent if no record	N/A	N/A	N/A

N/A, not applicable.

TABLE 38 Adjusted subdistribution HRs women in the derivation cohort for CFracture MOF

Predictor	Subdistribution HR	95% CI
$(\text{Age in years}/10)^2 - 28.7076$	1.1861	1.1821 to 1.1902
$(\text{Age in years}/10)^3 - 179.3379$	0.9872	0.9869 to 0.9876
$(\text{BMI}/10)^{-1} - 0.3914$	5.6848	5.0121 to 6.4478
Ethnicity		
South Asian	0.4235	0.3781 to 0.4745
Black African/Caribbean	0.2185	0.1974 to 0.2420
Other	0.3728	0.3251 to 0.4276
Alcohol intake		
Trivial (< 1 unit/day)	0.9953	0.9764 to 1.0145
Light (1–2 units/day)	1.0407	1.0116 to 1.0706
Moderate (3–6 units/day)	1.1315	1.0713 to 1.1951
Heavy (7–9 units/day)	1.3272	1.1514 to 1.5299
Very heavy (> 9 units/day)	1.2479	1.0818 to 1.4395

continued

TABLE 38 Adjusted subdistribution HRs women in the derivation cohort for CFracture MOF (*continued*)

Predictor	Subdistribution HR	95% CI
Smoking status		
Ex-smoker	1.0653	1.0444 to 1.0866
Light smoker	1.1055	1.0647 to 1.1479
Moderate smoker	1.1755	1.1350 to 1.2174
Heavy smoker	1.2051	1.1508 to 1.2619
Asthma or chronic obstructive airways disease	1.0710	1.0447 to 1.0981
Cancer	0.9753	0.9405 to 1.0114
CVD	0.9566	0.9340 to 0.9797
Dementia	0.7548	0.7195 to 0.7919
Epilepsy diagnosis or prescribed anti-convulsant	1.3021	1.2492 to 1.3572
History of falls	1.2502	1.2211 to 1.2800
Chronic liver disease	1.2872	1.1532 to 1.4368
Parkinson's disease	1.0518	0.9677 to 1.1431
Rheumatoid arthritis or SLE	1.1598	1.1045 to 1.2178
Chronic renal disease	0.8661	0.8179 to 0.9172
Type 1 diabetes	1.6056	1.4349 to 1.7966
Type 2 diabetes	1.0902	1.0532 to 1.1286
Prior fracture	1.6713	1.6347 to 1.7087
Endocrine disorders	0.9878	0.9252 to 1.0546
Malabsorption	1.1261	1.0644 to 1.1914
Parental history of osteoporosis or hip fracture	1.1306	1.0216 to 1.2512
Antidepressants	1.1875	1.1616 to 1.2140
Corticosteroids	1.1273	1.0794 to 1.1773
Oestrogen-only HRT	0.7642	0.7124 to 0.8198
CCI		
1	1.1160	1.0915 to 1.1410
2	1.1027	1.0712 to 1.1351
≥ 3	1.0528	1.0118 to 1.0955

HRT, hormone replacement therapy; SLE, systemic lupus erythematosus.

Note
Baseline 10-year CIF of 2.323,403% corresponding to the following baseline characteristics: aged 54 years, BMI of 25.5 kg/m^2, white or assumed white ethnicity, non-drinker, non-smoker and none of the above conditions.

TABLE 39 Adjusted subdistribution HRs men in the derivation cohort for CFracture MOF

Predictor	Subdistribution HR	95% CI
$(\text{Age in years}/10)^{0.5}$ – 2.410e-14	8.318e-03	5.184e-03 to 1.335e-02
(Age in years/10) – 6.376e-15	4.075	3.688 to 4.502
$(\text{BMI}/10)^{-1}$ + 6.372e-15	2.346e+08	1.584e+06 to 3.474e+10
$(\text{BMI}/10)^{0.5}$ – 2.303e-14	1.325e-09	2.706e-12 to 6.486e-07
Ethnicity		
South Asian	0.581	0.502 to 0.674
Black African/Caribbean	0.329	0.305 to 0.355
Other	0.357	0.296 to 0.431
Alcohol intake		
Trivial (< 1 unit/day)	0.956	0.910 to 1.003
Light (1–2 units/day)	0.964	0.925 to 1.004
Moderate (3–6 units/day)	1.008	0.951 to 1.069
Heavy (7–9 units/day)	1.282	1.149 to 1.431
Very heavy (> 9 units/day)	1.991	1.783 to 2.223
Smoking status		
Ex-smoker	1.063	1.026 to 1.101
Light smoker	1.226	1.127 to 1.333
Moderate smoker	1.284	1.221 to 1.349
Heavy smoker	1.286	1.227 to 1.347
Asthma or chronic obstructive airways disease	1.010	0.968 to 1.053
Cancer	1.010	0.952 to 1.070
CVD	0.938	0.903 to 0.975
Dementia	0.814	0.734 to 0.902
Epilepsy diagnosis or prescribed anti-convulsant	1.631	1.534 to 1.735
History of falls	1.438	1.367 to 1.512
Chronic liver disease	1.129	0.953 to 1.337
Parkinson's disease	1.415	1.268 to 1.580
Rheumatoid arthritis or SLE	1.354	1.212 to 1.512
Chronic renal disease	0.951	0.867 to 1.043
Type 1 diabetes	1.737	1.512 to 1.996
Type 2 diabetes	1.050	0.996 to 1.107
Prior fracture	2.126	2.035 to 2.221
Malabsorption	1.196	1.082 to 1.321
Care home resident	0.563	0.484 to 0.660
Parental history of osteoporosis	1.808	1.439 to 2.271
Antidepressants	1.305	1.246 to 1.366

continued

TABLE 39 Adjusted subdistribution HRs men in the derivation cohort for CFracture MOF (*continued*)

Predictor	Subdistribution HR	95% CI
Corticosteroids	1.116	1.023 to 1.217
CCI		
1	1.221	1.176 to 1.268
2	1.314	1.251 to 1.380
≥ 3	1.336	1.255 to 1.423

SLE, systemic lupus erythematosus.

Note
Baseline 10-year CIF of 1.325,196% corresponding to the following baseline characteristics: aged 47 years, BMI of 26 kg/m^2, white or assumed white ethnicity, non-drinker, non-smoker and none of the above conditions.

TABLE 40 Adjusted subdistribution HRs women in the derivation cohort for CFracture hip fracture

Predictor	Subdistribution HR	95% CI
(Age in years/10)^2 + 4.237e-13	1.4043	1.3913 to 1.4174
(Age in years/10)^3 + 4.225e-12	0.9750	0.9742 to 0.9758
(BMI/10)^2 – 5.803e-16	26.7979	20.0393 to 35.8359
Ethnicity		
South Asian	0.5776	0.4632 to 0.7201
Black African/Caribbean	0.3060	0.1929 to 0.4855
Other	0.5367	0.4172 to 0.6904
Alcohol intake		
Trivial (< 1 unit/day)	0.9424	0.9129 to 0.9728
Light (1–2 units/day)	0.9775	0.9423 to 1.0141
Moderate (3–6 units/day)	1.0302	0.9354 to 1.1345
Heavy (7–9 units/day)	1.1886	0.9149 to 1.5441
Very heavy (> 9 units/day)	1.3425	1.0004 to 1.8015
Smoking status		
Ex-smoker	1.0350	1.0027 to 1.0684
Light smoker	1.1938	1.1150 to 1.2781
Moderate smoker	1.2787	1.2004 to 1.3620
Heavy smoker	1.4071	1.3133 to 1.5075
Asthma or chronic obstructive airways disease	1.0419	1.0022 to 1.0831
Cancer	0.9496	0.9008 to 1.0011
CVD	0.9763	0.9444 to 1.0092
Dementia	0.9237	0.8721 to 0.9783
Epilepsy diagnosis or prescribed anti-convulsant	1.2616	1.1828 to 1.3458
History of falls	1.2174	1.1772 to 1.2590
Chronic liver disease	1.3347	1.1199 to 1.5908
Parkinson's disease	1.2782	1.1540 to 1.4157

TABLE 40 Adjusted subdistribution HRs women in the derivation cohort for CFracture hip fracture (*continued*)

Predictor	Subdistribution HR	95% CI
Rheumatoid arthritis or SLE	1.3488	1.2583 to 1.4459
Chronic renal disease	0.8515	0.7886 to 0.9195
Type 1 diabetes	2.2159	1.8568 to 2.6444
Type 2 diabetes	1.1742	1.1170 to 1.2343
Prior fracture	1.4615	1.4148 to 1.5098
Endocrine disorders	1.1495	1.0467 to 1.2623
Antidepressants	1.1790	1.1392 to 1.2202
Corticosteroids	1.0418	0.9762 to 1.1118
Oestrogen-only HRT	0.7794	0.6784 to 0.8955
CCI		
1	1.1250	1.0869 to 1.1644
2	1.1160	1.0691 to 1.1650
≥ 3	1.0739	1.0140 to 1.1373

HRT, hormone replacement therapy; SLE, systemic lupus erythematosus.

Note
Baseline 10-year CIF of 0.2,336,889% corresponding to the following baseline characteristics: aged 54 years, BMI of 25.1 kg/m^2, white or assumed white ethnicity, non-drinker, non-smoker and none of the above conditions.

TABLE 41 Adjusted subdistribution HRs men in the derivation cohort for CFracture hip fracture

Predictor	Subdistribution HR	95% CI
(Age in years/10)^3 + 3.047e-12	1.0489	1.0464 to 1.0515
(Age in years/10)^3 × log(Age in years/10) + 3.317e-12	0.9818	0.9808 to 0.9829
(BMI/10)^2 – 1.723e-15	187.7101	106.6578 to 330.3562
Ethnicity		
South Asian	0.4936	0.3661 to 0.6656
Black African/Caribbean	0.2640	0.1318 to 0.5287
Other	0.5366	0.3806 to 0.7565
Alcohol intake		
Trivial (< 1 unit/day)	0.9275	0.8706 to 0.9882
Light (1–2 units/day)	0.8902	0.8348 to 0.9492
Moderate (3–6 units/day)	0.9585	0.8847 to 1.0386
Heavy (7–9 units/day)	1.2728	1.1157 to 1.4520
Very heavy (> 9 units/day)	1.7853	1.4829 to 2.1494
Smoking status		
Ex-smoker	1.0666	1.0106 to 1.1257
Light smoker	1.3543	1.2301 to 1.4909
Moderate smoker	1.4657	1.3361 to 1.6078
Heavy smoker	1.5036	1.3826 to 1.6351

continued

TABLE 41 Adjusted subdistribution HRs men in the derivation cohort for CFracture hip fracture (*continued*)

Predictor	Subdistribution HR	95% CI
Asthma or chronic obstructive airways disease	0.9623	0.9040 to 1.0243
Cancer	0.9402	0.8699 to 1.0163
CVD	0.9100	0.8637 to 0.9589
Dementia	1.1374	1.0107 to 1.2799
Epilepsy diagnosis or prescribed anti-convulsant	1.7134	1.5641 to 1.8770
History of falls	1.4025	1.3083 to 1.5034
Chronic liver disease	1.2790	0.9728 to 1.6816
Parkinson's disease	1.7864	1.5671 to 2.0363
Rheumatoid arthritis or SLE	1.4296	1.2268 to 1.6660
Chronic renal disease	1.1160	0.9951 to 1.2514
Type 1 diabetes	2.4706	2.0042 to 3.0455
Type 2 diabetes	1.0826	1.0064 to 1.1644
Prior fracture	1.9079	1.7758 to 2.0498
Care home resident	0.7210	0.5987 to 0.8682
Parental history of osteoporosis or hip fracture	1.0542	0.6810 to 1.6320
Antidepressants	1.2116	1.1276 to 1.3018
Corticosteroids	0.9206	0.8105 to 1.0457
CCI		
1	1.2446	1.1741 to 1.3193
2	1.3116	1.2226 to 1.4070
≥ 3	1.3630	1.2479 to 1.4887

SLE, systemic lupus erythematosus.

Note
Baseline 10-year CIF of 0.2,110,133% corresponding to the following baseline characteristics: aged 53 years, BMI of 26.2 kg/m^2, white or assumed white ethnicity, non-drinker, non-smoker and none of the above conditions.

TABLE 42 Baseline data in fracture data set for men and women compared with original QFracture-2012 internal validation cohort (reports total population data only)[4]

Data	External validation cohort		All patients QFracture-2012 internal validation (*N* = 1,583,373)
	Women external validation cohort (*N* = 2,747,409; 50.6%)	Men (*N* = 2,684,730; 49.4%)	
Age (years), mean (SD)	50.7 (17.4)	48.5 (15.6)	50 (1.6)
BMI (kg/m^2), mean (SD)	26.6 (6.0)	27.1 (4.8)	26.1 (4.6)
Women, *n* (%)	2,747,409 (50.6)		804,563 (50.8)
Ethnicity, *n* (%)			
White or not recorded	2,614,423 (95.2)	2,556,923 (95.2)	1,493,455 (94.3)
Indian	25,420 (0.9)	27,087 (1.0)	17,670 (1.1)
Pakistani	11,121 (0.4)	12,316 (0.5)	6489 (0.4)

TABLE 42 Baseline data in fracture data set for men and women compared with original QFracture-2012 internal validation cohort (reports total population data only)[4] (*continued*)

Data	External validation cohort		All patients QFracture-2012 internal validation (*N* = 1,583,373)
	Women external validation cohort (*N* = 2,747,409; 50.6%)	Men (*N* = 2,684,730; 49.4%)	
Bangladeshi	3473 (0.1)	4972 (0.2)	4191 (0.3)
Other Asian	18,896 (0.7)	17,758 (0.7)	10,779 (0.7)
Black Caribbean	4780 (0.2)	4030 (0.2)	10,144 (0.6)
Black African	22,736 (0.8)	20,776 (0.8)	17,367 (1.1)
Chinese	7358 (0.3)	5517 (0.2)	5206 (0.3)
Other ethnic group	39,202 (1.4)	35,351 (1.3)	18,072 (1.1)
Smoking status, *n* (%)			
Non-smoker	1,146,025 (58.3)	807,294 (46.9)	773,198 (48.8)
Ex-smoker	390,520 (19.9)	439,503 (25.5)	257,087 (16.2)
Light (< 10 cigarettes/day)	135,272 (6.9)	125,229 (7.3)	94,400 (6.0)
Moderate (10–19 cigarettes/day)	188,078 (9.6)	190,990 (11.1)	113,757 (7.2)
Heavy (20 + cigarettes/day)	107,288 (5.5)	158,134 (9.2)	86,787 (5.5)
Current smoking amount not recorded	43,957 (11.5)	78,372 (23.3)	65,106 (4.1)
Not recorded	780,226 (28.4)	963,580 (35.9)	193,038 (12.2)
Alcohol status			
None	570,900 (27.9)	317,208 (17.4)	330,695 (20.9)
< 1 unit/day	854,476 (41.7)	548,761 (30.2)	402,847 (25.4)
1–2 units/day	561,603 (27.4)	669,776 (36.8)	287,441 (18.2)
3–6 units/day	52,785 (2.6)	224,507 (12.3)	84,478 (5.3)
7–9 units/day	5750 (0.3)	38,273 (2.1)	8743 (0.6)
> 9 units/day	2993 (0.1)	9583 (1.1)	7429 (0.5)
Not recorded	698,902 (25.4)	866,622 (32.3)	461,740 (29.2)
Previous MOF	152,417 (5.5)	113,520 (4.2)	27,907 (1.8)
Parental history of osteoporosis or hip fracture	10,561 (0.4)	1077 (0.04)	4227 (0.3)
Nursing or care home resident	16,819 (0.6)	7455 (0.3)	1535 (0.1)
Condition or prescription			
Type 1 diabetes	8747 (0.3)	12,008 (0.4)	4322 (0.3)
Type 2 diabetes	81,715 (3.0)	100,009 (3.7)	43,437 (2.7)
History of falls	153,841 (5.6)	74,368 (2.8)	17,382 (1.1)
Dementia	34,892 (1.3)	15,036 (0.6)	7791 (0.5)
Cancer	94,090 (3.4)	67,380 (2.5)	28,203 (1.8)
Asthma or COPD	355,014 (12.9)	303,541 (11.3)	113,175 (7.1)
CVD	156,577 (5.7)	195,378 (7.3)	77,824 (4.9)

continued

TABLE 42 Baseline data in fracture data set for men and women compared with original QFracture-2012 internal validation cohort (reports total population data only)[4] (*continued*)

Data	External validation cohort		All patients QFracture-2012 internal validation (*N* = 1,583,373)
	Women external validation cohort (*N* = 2,747,409; 50.6%)	Men (*N* = 2,684,730; 49.4%)	
Chronic liver disease	6093 (0.2)	6753 (0.3)	3216 (0.2)
Chronic renal disease	33,274 (1.2)	24,395 (0.9)	3413 (0.2)
Parkinson's disease	7585 (0.3)	8348 (0.3)	3650 (0.2)
Rheumatoid arthritis or SLE	11,970 (0.4)	32,950 (1.2)	10,091 (0.6)
Malabsorption	34,884 (1.3)	27,122 (1.0)	8026 (0.5)
Endocrine disorders	25,089 (0.9)	5866 (0.2)	7882 (0.5)
Epilepsy or prescribed anticonvulsants	66,145 (2.4)	59,214 (2.2)	26,271 (1.7)
Prescribed antidepressants	66,145 (2.4)	59,214 (2.2)	111,229 (7.0)
Prescribed corticosteroid	37,169 (1.4)	22,632 (0.8)	30,998 (2.0)
Prescribed oestrogen-only HRT	33,679 (1.2)	127 (0.0)	14,988 (0.9)

COPD, chronic obstructive pulmonary disease; HRT, hormone replacement therapy; SD, standard deviation; SLE, systemic lupus erythematosus.
Source: Livingstone *et al.*[50]

TABLE 43 Crude incidence of MOF over 10 years of follow-up

Age range (years)	Women			Men		
	Incident MOF	Total follow-up (years)	Rate per 1000 person-year (95% CI)	Incident MOF	Total follow-up (years)	Rate per 1000 person-years (95% CI)
30–34	2603	2,741,657	0.95 (0.91 to 0.99)	2828	2,784,175	1.02 (0.98 to 1.05)
35–39	2025	1,870,595	1.08 (1.04 to 1.13)	2121	1,927,589	1.10 (1.05 to 1.15)
40–44	2698	1,833,507	1.47 (1.42 to 1.53)	2222	1,917,796	1.16 (1.11 to 1.21)
45–49	3633	1,595,805	2.28 (2.20 to 2.35)	2239	1,681,808	1.33 (1.28 to 1.39)
50–54	5292	1,449,369	3.65 (3.55 to 3.75)	2248	1,497,499	1.50 (1.44 to 1.56)
55–59	7422	1,490,080	4.98 (4.87 to 5.10)	2644	1,505,675	1.76 (1.69 to 1.82)
60–64	7762	1,210,157	6.41 (6.27 to 6.56)	2743	1,191,801	2.30 (2.22 to 2.39)
65–69	9455	1,024,227	9.23 (9.05 to 9.42)	2859	960,815	2.98 (2.87 to 3.09)
70–74	11,757	861,260	13.65 (13.41 to 13.90)	3456	748,844	4.62 (4.46 to 4.77)
75–80	14,148	688,855	20.54 (20.21 to 20.88)	4068	516,507	7.88 (7.64 to 8.12)
80–84	14,653	508,415	28.82 (28.36 to 29.28)	3891	304,005	12.80 (12.41 to 13.20)
85–90	9017	237,728	37.93 (37.17 to 38.71)	2080	107,018	19.44 (18.63 to 20.28)
90–99	5133	112,888	45.47 (44.27 to 46.70)	922	36,093	25.55 (23.97 to 27.22)
Total	95,598	15,624,543	6.12 (6.08 to 6.16)	34,321	15,179,623	2.26 (2.24 to 2.29)

Source: Livingstone *et al.*[50]

TABLE 44 Crude incidence of hip fracture over 10 years of follow-up

	Women			Men		
Age range (years)	Incident hip fractures	Total follow-up (years)	Rate per 1000 person-years (95% CI)	Incident hip fractures	Total follow-up (years)	Rate per 1000 person-years (95% CI)
30–34	93	2,750,441	0.03 (0.03 to 0.04)	214	2,793,615	0.08 (0.07 to 0.09)
35–39	109	1,878,222	0.06 (0.05 to 0.07)	223	1,935,329	0.12 (0.10 to 0.13)
40–44	183	1,842,965	0.10 (0.09 to 0.11)	307	1,925,573	0.16 (0.14 to 0.18)
45–49	374	1,607,632	0.23 (0.21 to 0.26)	377	1,689,307	0.22 (0.20 to 0.25)
50–54	599	1,467,062	0.41 (0.38 to 0.44)	442	1,504,825	0.29 (0.27 to 0.32)
55–59	1149	1,515,268	0.76 (0.72 to 0.80)	701	1,513,119	0.46 (0.43 to 0.50)
60–64	1554	1,234,523	1.26 (1.20 to 1.32)	948	1,197,990	0.79 (0.74 to 0.84)
65–69	2614	1,051,678	2.49 (2.39 to 2.58)	1217	966,352	1.26 (1.19 to 1.33)
70–74	4460	889,669	5.01 (4.87 to 5.16)	1709	754,325	2.27 (2.16 to 2.38)
75–80	6905	715,572	9.65 (9.43 to 9.88)	2432	521,184	4.67 (4.48 to 4.86)
80–84	8752	527,816	16.58 (16.24 to 16.93)	2640	307,196	8.59 (8.27 to 8.93)
85–90	5968	246,247	24.24 (23.64 to 24.85)	1469	108,226	13.57 (12.90 to 14.28)
90–99	3640	115,681	31.47 (30.48 to 32.49)	700	36,423	19.22 (17.86 to 20.68)
Total	36,400	15,842,775	2.30 (2.27 to 2.32)	13,379	15,253,462	0.88 (0.86 to 0.89)

Source: Livingstone *et al.*[50]

TABLE 45 Crude incidence of non-fracture death over 10 years of follow-up

	Women			Men		
Age range (years)	Incident non-fracture death	Total follow-up (years)	Rate per 1000 person-years (95% CI)	Incident non-fracture death	Total follow-up (years)	Rate per 1000 person-years (95% CI)
30–34	1348	2,741,657	0.49 (0.47 to 0.52)	2346	2,784,175	0.84 (0.81 to 0.88)
35–39	1677	1,870,595	0.90 (0.85 to 0.94)	2411	1,927,589	1.25 (1.20 to 1.30)
40–44	2534	1,833,507	1.38 (1.33 to 1.44)	3605	1,917,796	1.88 (1.82 to 1.94)
45–49	3714	1,595,805	2.33 (2.25 to 2.40)	5094	1,681,808	3.03 (2.95 to 3.11)
50–54	4991	1,449,369	3.44 (3.35 to 3.54)	7398	1,497,499	4.94 (4.83 to 5.05)
55–59	7996	1,490,080	5.37 (5.25 to 5.48)	12,167	1,505,675	8.08 (7.94 to 8.23)
60–64	10,378	1,210,157	8.58 (8.41 to 8.74)	15,427	1,191,801	12.94 (12.74 to 13.15)
65–69	14,216	1,024,227	13.88 (13.65 to 14.11)	20,779	960,815	21.63 (21.34 to 21.92)
70–74	19,734	861,260	22.91 (22.60 to 23.23)	26,842	748,844	35.84 (35.43 to 36.27)
75–80	27,874	688,855	40.46 (40.00 to 40.93)	31,087	516,507	60.19 (59.54 to 60.84)
80–84	36,030	508,415	70.87 (70.17 to 71.58)	30,228	304,005	99.43 (98.37 to 100.50)
85–89	29,415	237,728	123.73 (122.42 to 125.06)	16,832	107,018	157.28 (155.11 to 159.48)
90–99	23,799	112,888	210.82 (208.45 to 213.21)	8865	36,093	245.62 (241.20 to 250.09)
Total	183,706	15,624,543	11.76 (11.70 to 11.81)	183,081	15,179,623	12.06 (12.01 to 12.12)

Source: Livingstone *et al.*[50]

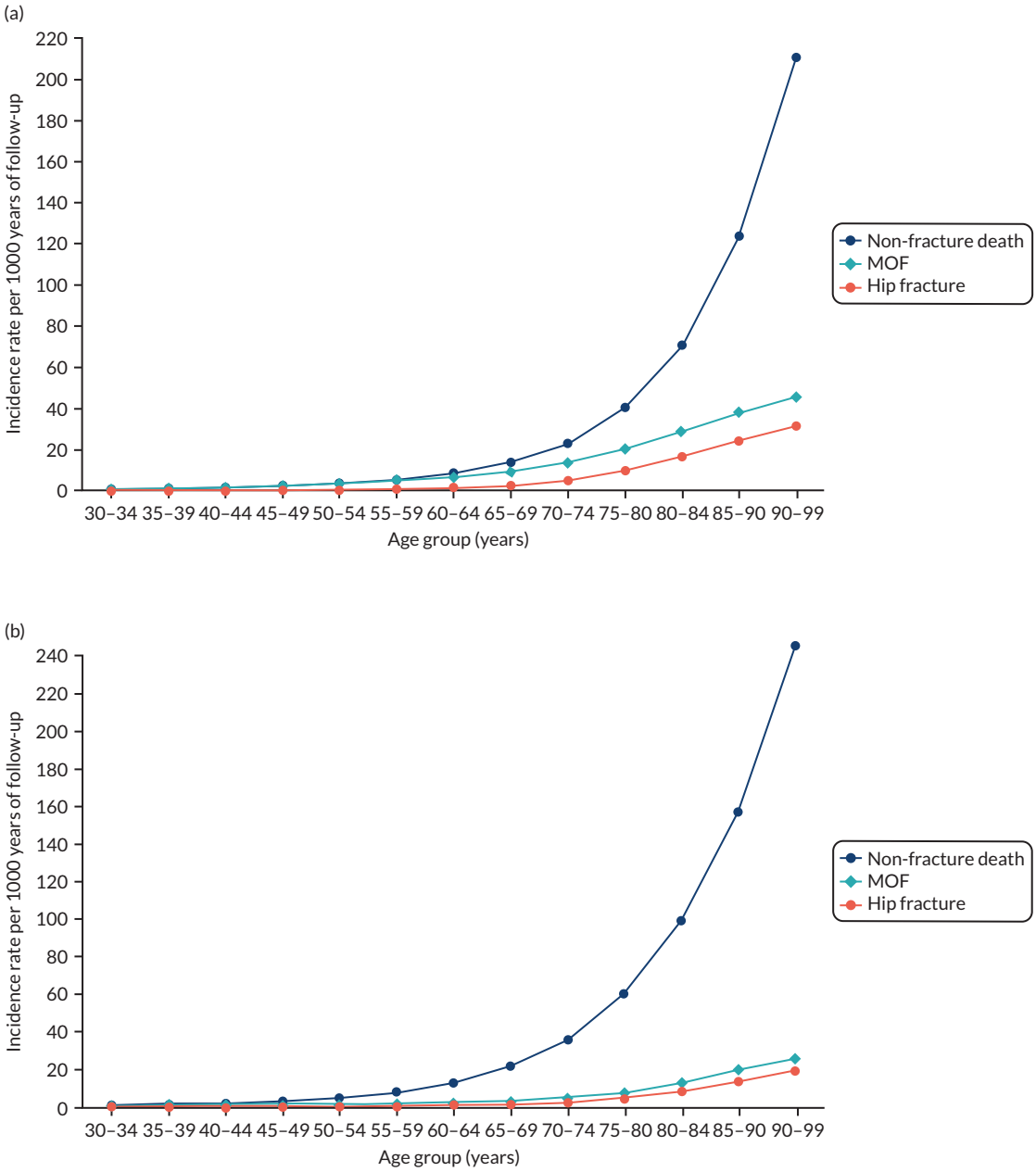

FIGURE 32 Major osteoporotic fracture, hip fracture and non-fracture death incidence in (a) women; and (b) men. Source: Livingstone *et al.*[50]

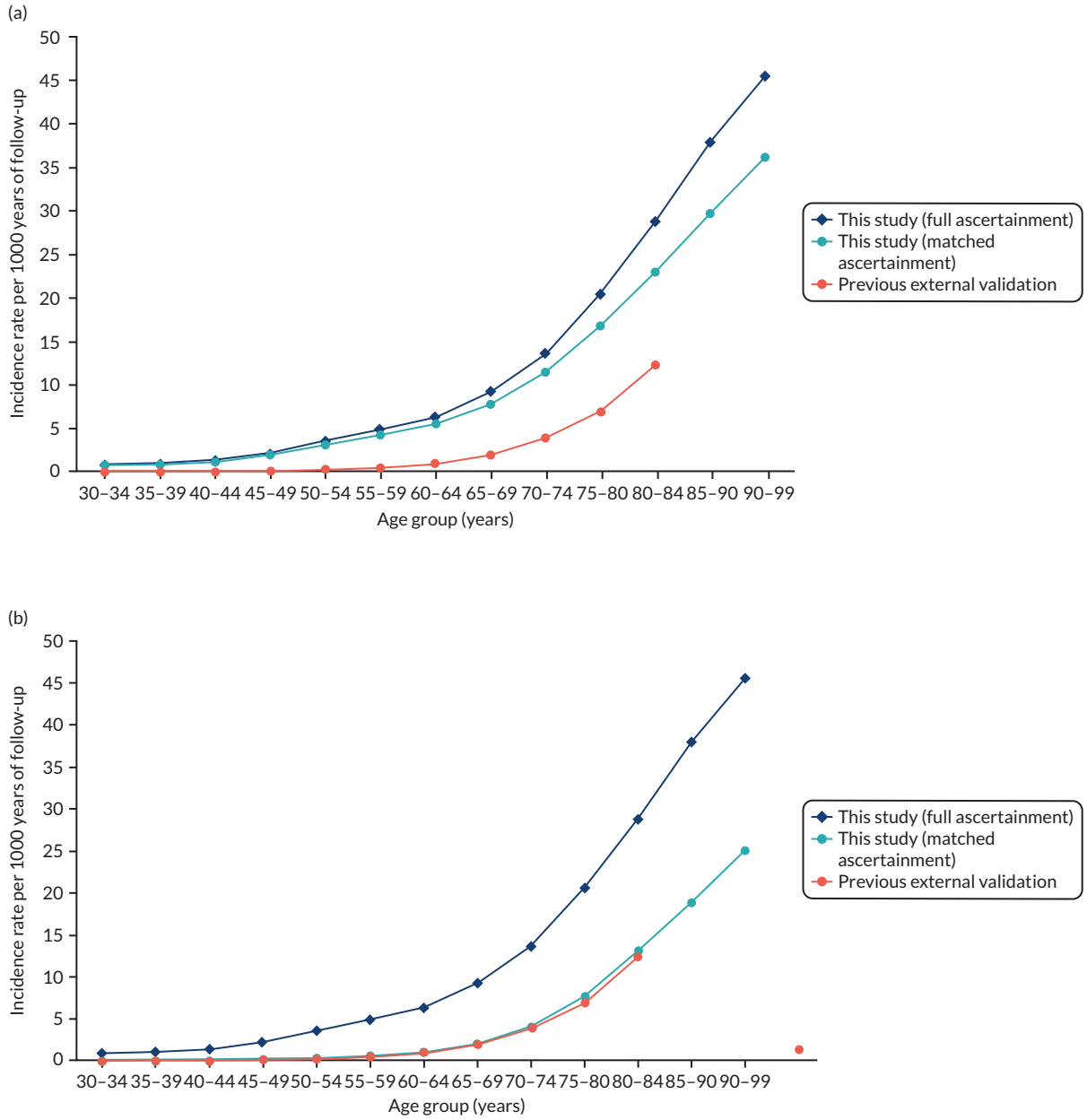

FIGURE 33 Comparison of fracture incidence in this study (using GP, mortality and hospital admission data), previous external validation (using GP and ONS data, but maximum age 85 years) and this study matched to previous external validation ascertainment (using GP and ONS data). (a) Women: MOFs; (b) women: hip fractures; (c) men: MOFs; and (d) men: hip fractures. Source: Livingstone *et al.*[50] (*continued*)

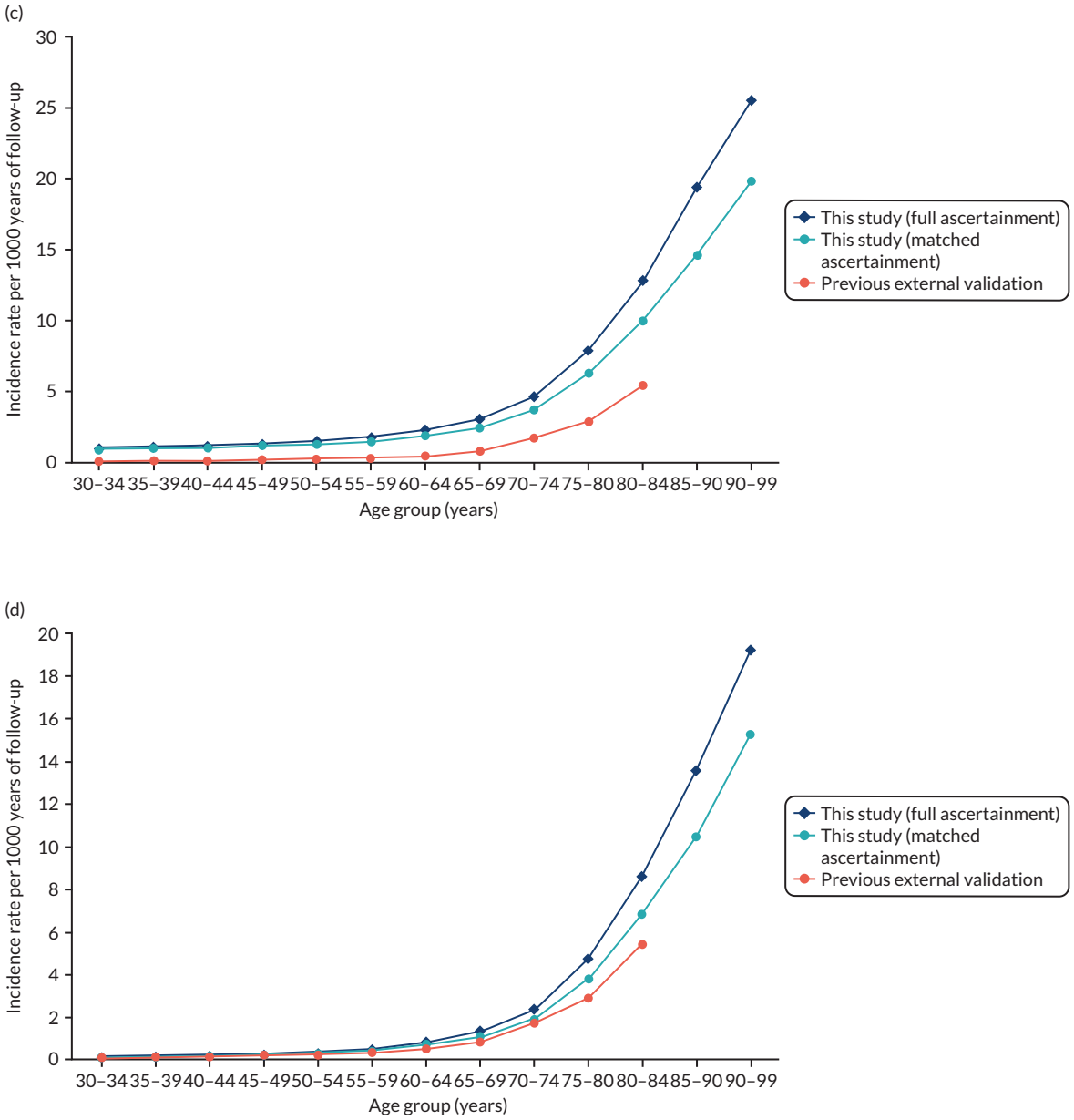

FIGURE 33 Comparison of fracture incidence in this study (using GP, mortality and hospital admission data), previous external validation (using GP and ONS data, but maximum age 85 years) and this study matched to previous external validation ascertainment (using GP and ONS data). (a) Women: MOFs; (b) women: hip fractures; (c) men: MOFs; and (d) men: hip fractures. Source: Livingstone *et al.*[50]

Appendix 5 Direct treatment disutility elicitation: supplementary results

TABLE 46 Count data (normalised) for best and worst scores

	Bisphosphonates									Statins								
	Experience of taking bisphosphonates (*n* = 83)			No experience of taking bisphosphonates (*n* = 229)			Pooled (*n* = 312)			Experience of taking statins (*n* = 105)			No experience of taking statins (*n* = 214)			Pooled (*n* = 319)		
Attribute level	Best	Worst	Best–worst	Best	Worst	Best–worst	Best	Worst	Best–worst	Best	Worst	Best–worst	Best	Worst	Best–worst	Best	Worst	Best–worst
No inconvenience	0.76	0.11	0.65	0.62	0.15	0.47	0.65	0.15	0.50	0.62	0.15	0.47	0.65	0.15	0.50	0.64	0.15	0.49
Inconvenience	0.62	0.22	0.40	0.61	0.17	0.45	0.56	0.19	0.37	0.61	0.17	0.45	0.56	0.19	0.37	0.58	0.18	0.39
MSE																		
1%	0.15	0.17	−0.02	0.24	0.23	0.00	0.23	0.25	−0.02	0.24	0.23	0.00	0.23	0.25	−0.02	0.23	0.25	−0.01
5%	0.16	0.22	−0.05	0.20	0.36	−0.16	0.17	0.37	−0.20	0.20	0.36	−0.16	0.17	0.37	−0.20	0.18	0.37	−0.19
9%	0.16	0.28	−0.12	0.20	0.38	−0.19	0.16	0.46	−0.29	0.20	0.38	−0.19	0.16	0.46	−0.29	0.17	0.43	−0.26
13%	0.14	0.28	−0.13	0.19	0.43	−0.24	0.18	0.49	−0.32	0.19	0.43	−0.24	0.18	0.49	−0.32	0.18	0.47	−0.29
SSE																		
0.1%	0.14	0.58	−0.44	0.20	0.46	−0.27	0.28	0.37	−0.09	0.20	0.46	−0.27	0.28	0.37	−0.09	0.25	0.40	−0.15
0.3%	0.17	0.60	−0.42	0.16	0.49	−0.32	0.21	0.43	−0.22	0.16	0.49	−0.32	0.21	0.43	−0.22	0.19	0.45	−0.25
0.5%	0.16	0.61	−0.45	0.17	0.50	−0.34	0.17	0.46	−0.29	0.17	0.50	−0.34	0.17	0.46	−0.29	0.17	0.47	−0.31
0.7%	0.14	0.60	−0.46	0.19	0.50	−0.31	0.18	0.49	−0.31	0.19	0.50	−0.31	0.18	0.49	−0.31	0.19	0.50	−0.31

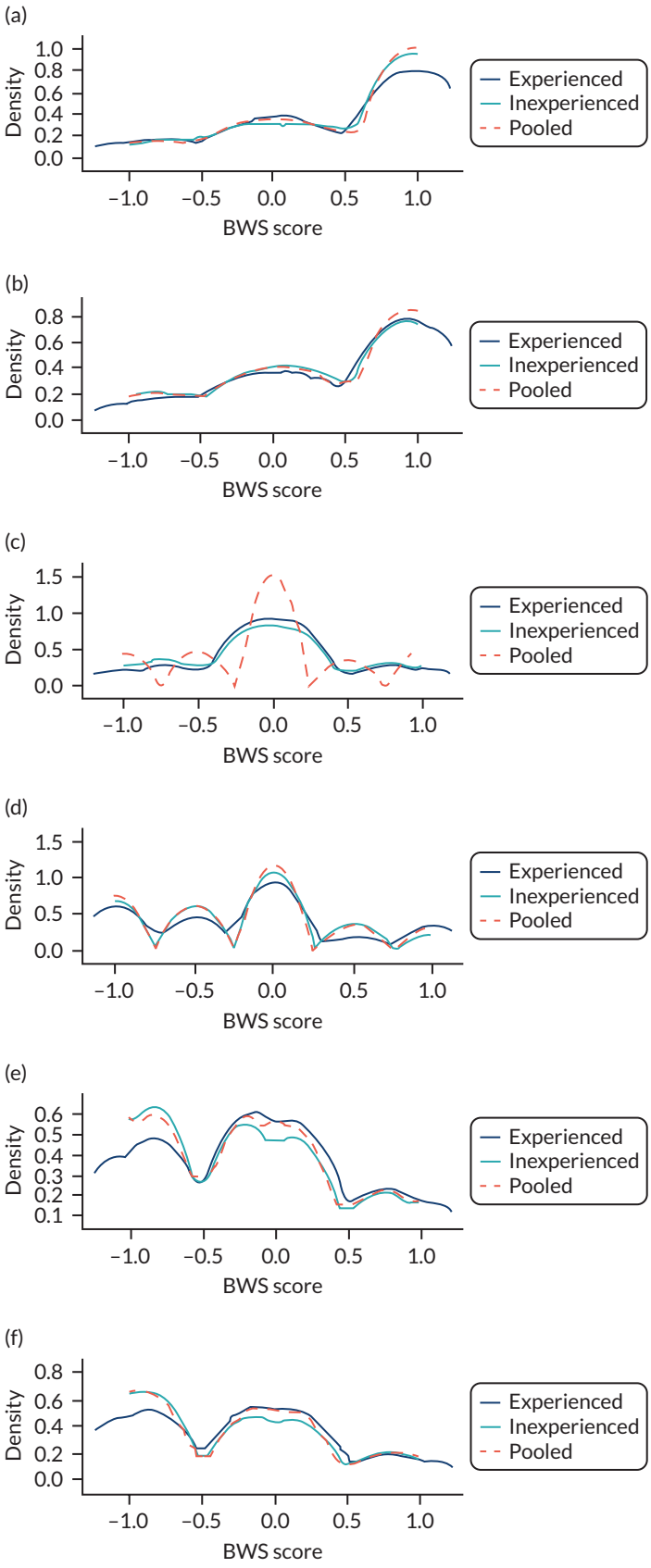

FIGURE 34 Kernel density plots showing distribution of BWS responses stratified by question context and respondent type: statins. (a) No inconvenience; (b) inconvenience; (c) MSE 1%; (d) MSE 5%; (e) MSE 9%; (f) MSE 13%; (g) SSE 0.1%; (h) SSE 0.3%; (i) SSE 0.5%; and (j) SSE 0.7%. (*continued*)

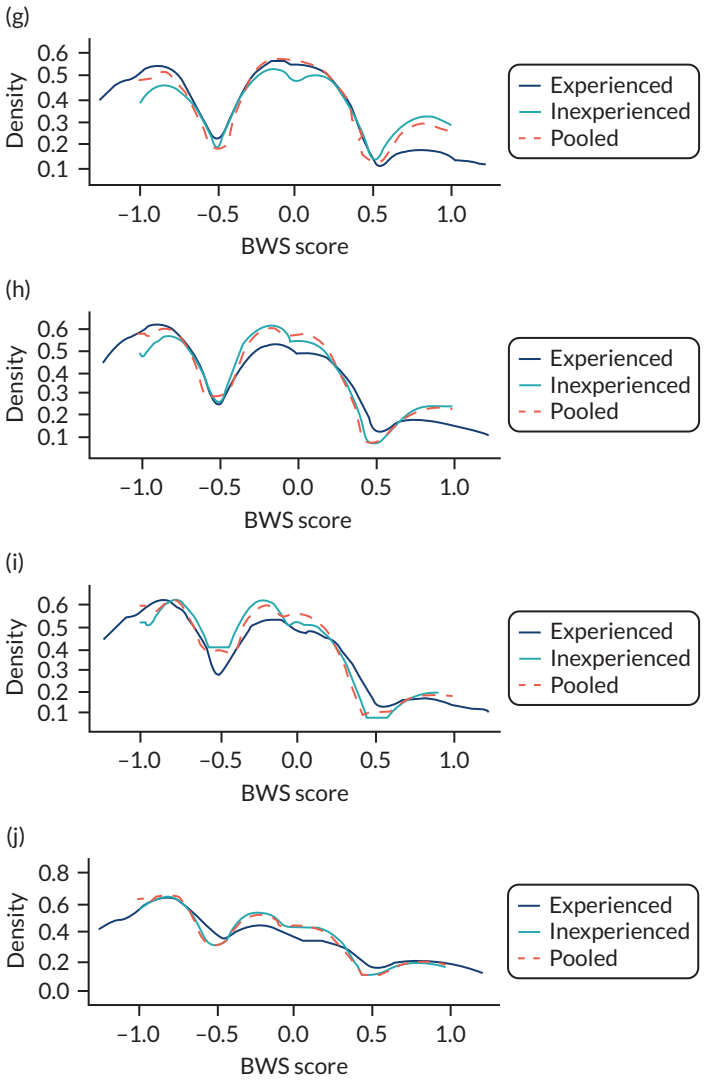

FIGURE 34 Kernel density plots showing distribution of BWS responses stratified by question context and respondent type: statins. (a) No inconvenience; (b) inconvenience; (c) MSE 1%; (d) MSE 5%; (e) MSE 9%; (f) MSE 13%; (g) SSE 0.1%; (h) SSE 0.3%; (i) SSE 0.5%; and (j) SSE 0.7%.

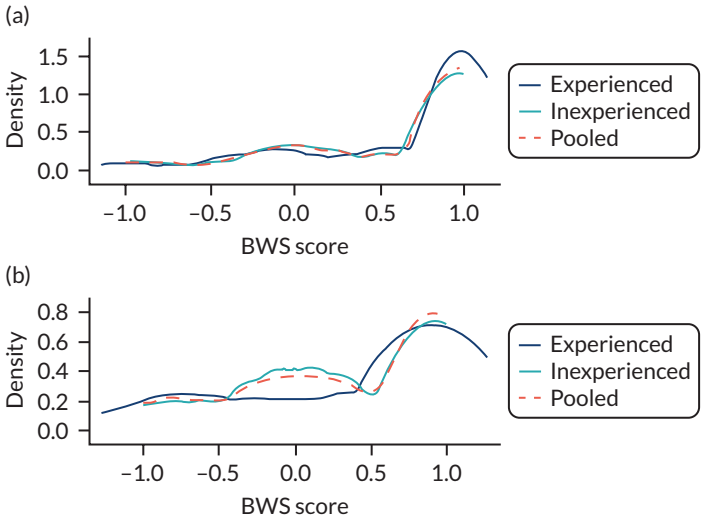

FIGURE 35 Kernel density plots showing distribution of BWS responses stratified by question context and respondent type: bisphosphonates. (a) No inconvenience; (b) inconvenience; (c) MSE 1%; (d) MSE 5%; (e) MSE 9%; (f) MSE 13%; (g) SSE 0.1%; (h) SSE 0.3%; (i) SSE 0.5%; and (j) SSE 0.7%. (*continued*)

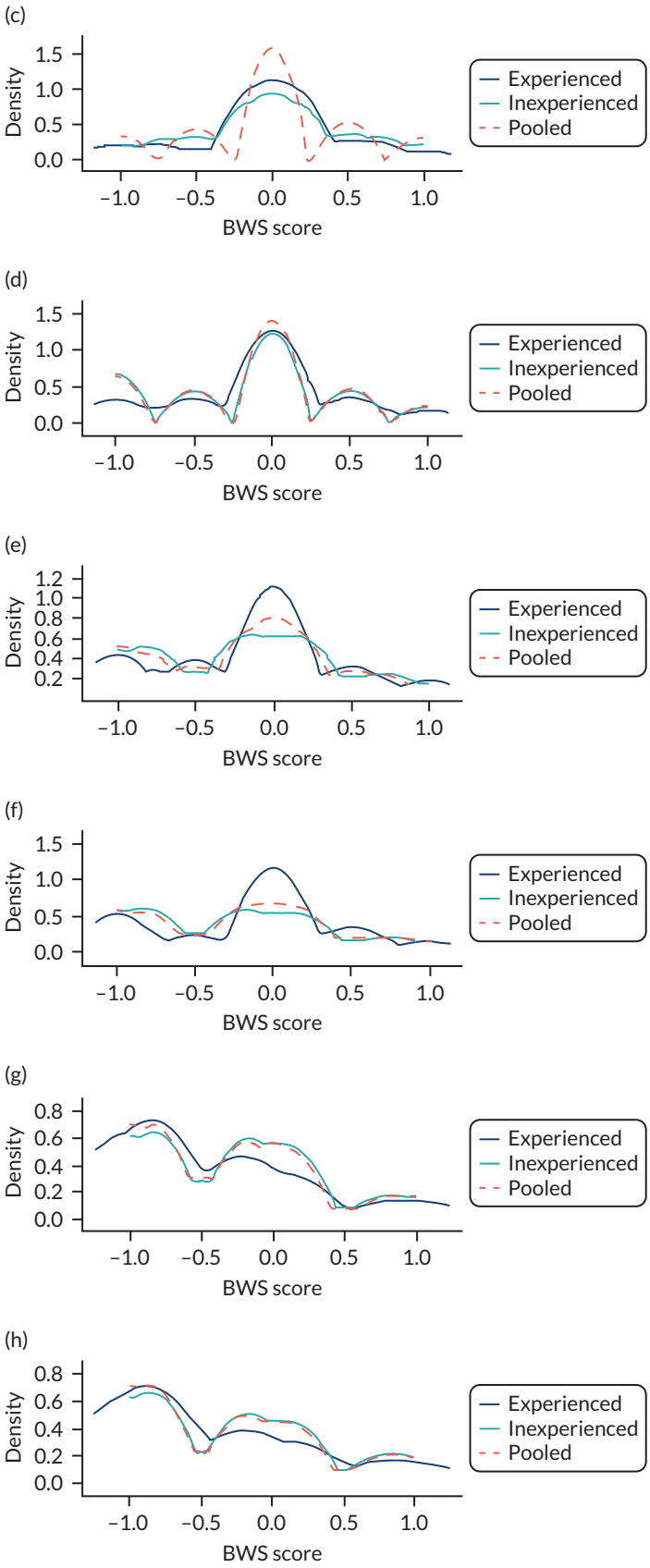

FIGURE 35 Kernel density plots showing distribution of BWS responses stratified by question context and respondent type: statins. (a) No inconvenience; (b) inconvenience; (c) MSE 1%; (d) MSE 5%; (e) MSE 9%; (f) MSE 13%; (g) SSE 0.1%; (h) SSE 0.3%; (i) SSE 0.5%; and (j) SSE 0.7%. (*continued*)

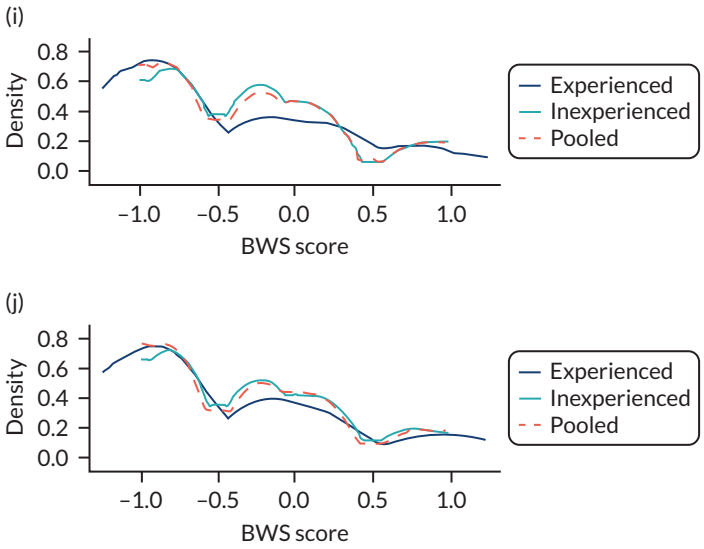

FIGURE 35 Kernel density plots showing distribution of BWS responses stratified by question context and respondent type: statins. (a) No inconvenience; (b) inconvenience; (c) MSE 1%; (d) MSE 5%; (e) MSE 9%; (f) MSE 13%; (g) SSE 0.1%; (h) SSE 0.3%; (i) SSE 0.5%; and (j) SSE 0.7%.

Appendix 6 Supplementary methods for model assessing cost-effectiveness of statins for the primary prevention of cardiovascular disease

Type of first cardiovascular event

We fitted a multinomial logistic regression model to the CPRD data set (which excluded people who have previously experienced cardiovascular events or received statins) to estimate the relative probabilities of a cardiovascular event being of each type, according to sex, age at event and baseline QRISK3-predicted risk. Multinomial logistic regression provides a way of predicting the likelihood of each of a number of possible events in a single statistical model. In logistic regression, the probabilities of each event are output as log-transformed odds of the events against a reference event. Accordingly, for each included risk factor, the model estimates a separate coefficient for each event, which can be interpreted as a log-transformed OR. Exponentiating these coefficients gives the ratios by which a unit change of the corresponding risk factors changes the odds of the event against the reference.

Table 47 shows the output from the multinomial regression model that we constructed, for which cardiovascular death was the reference event. Applying the coefficient values for an event type to a set of covariate values reflecting a cohort's risk factors gives the log-odds between that event and cardiovascular death for the cohort.

To give a worked example, consider 50-year-old women with a 10-year QRISK3-predicted CVD risk of 10%. For women in this subgroup who experience a cardiovascular event, we can calculate the log-odds that this event will be a MI compared with cardiovascular death as follows. For each unit of age, one unit of the corresponding coefficient for MI (set at its mean value) is added (not multiplied because, before exponentiation, we are working on a logarithmic scale) to the intercept: $4.2883 + 50 \times -0.1052$. For women, we do not apply the 'male' coefficient. The transformations and interactions described in *Table 47* must be applied to age, sex and QRISK3-predicted risk before applying all other coefficients in the same way. Let I be the set of cohort characteristics (i.e. women, 50 years old, 10% QRISK3). Therefore, the final equation is:

$$\log\left(\frac{P(\mathrm{MI})_I}{P(\mathrm{CV\,death})_I}\right) = 4.2883 + \mathrm{logit}\,(0.1) \times 1.3078 + 50 \times -0.1052 + 50^2 \times 0.0006 + 50 \times \mathrm{logit}\,(0.1) \times -0.0498 + 50^2 \times \mathrm{logit}\,(0.1) \times 0.0003 = 1.17. \quad (6)$$

We exponentiate to give the odds of MI against non-cardiovascular death for covariates I:

$$\frac{P(\mathrm{MI})_I}{P(\mathrm{CV\,death})_I} = \exp\,(1.17) = 3.22. \quad (7)$$

Once we have calculated the odds of each event against the reference, we may calculate the absolute probabilities of each event as follows. First, we express the absolute probability of the event being a MI as a multiple of the absolute probability of the event being cardiovascular death:

$$P(\mathrm{MI})_I = 3.22 \times P(\mathrm{CV\,death})_I. \quad (8)$$

TABLE 47 Multinomial regression estimating type of first cardiovascular event as a function of age at event, sex and cardiovascular risk

	MI		SA		Stroke		TIA		UA	
Parameter	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Intercept	4.28826	4.28812 to 4.28840	−0.08864	−0.08877 to −0.08851	−3.91704	−3.91717 to −3.91692	−5.49010	−5.49024 to −5.48996	5.85206	5.85192 to 5.85219
Male	−0.27917	−0.27934 to −0.27900	−0.97014	−0.97029 to −0.96998	−0.42471	−0.42488 to −0.42454	0.53725	0.53707 to 0.53744	−2.19771	−2.19781 to −2.19761
Logit(QRISK3)	1.30783	1.30769 to 1.30798	0.63785	0.63772 to 0.63799	−0.64463	−0.64479 to −0.64447	−0.48442	−0.48459 to −0.48426	1.74833	1.74819 to 1.74846
Age	−0.10524	−0.11121 to −0.09927	0.04209	0.03676 to 0.04742	0.08843	0.08285 to 0.09401	0.12395	0.11794 to 0.12996	−0.17737	−0.18239 to −0.17234
Age^2	0.00057	0.00049 to 0.00064	−0.00052	−0.00059 to −0.00045	−0.00050	−0.00057 to −0.00043	−0.00079	−0.00087 to −0.00072	0.00100	0.00094 to 0.00106
Male × logit (QRISK3)	−0.29154	−0.29170 to −0.29138	−0.82318	−0.82332 to −0.82303	−0.39047	−0.39064 to −0.39030	−0.27136	−0.27154 to −0.27119	−1.17876	−1.17890 to −1.17861
Age × male	0.03327	0.02666 to 0.03987	0.02899	0.02288 to 0.03510	0.02439	0.01767 to 0.03112	−0.00780	−0.01514 to −0.00046	0.07193	0.06816 to 0.07569
Age^2 × male	−0.00033	−0.00042 to −0.00025	−0.00019	−0.00027 to −0.00012	−0.00025	−0.00033 to −0.00017	0.00001	−0.00008 to 0.00010	−0.00054	−0.00059 to −0.00048
Age × logit (QRISK3)	−0.04975	−0.05214 to −0.04736	−0.03331	−0.03553 to −0.03108	−0.00323	−0.00546 to −0.00099	−0.01097	−0.01328 to −0.00867	−0.06871	−0.07124 to −0.06618
Age^2 × logit (QRISK3)	0.00034	0.00030 to 0.00038	0.00024	0.00020 to 0.00028	0.00006	0.00003 to 0.00010	0.00011	0.00007 to 0.00014	0.00050	0.00045 to 0.00054
Age × male × logit (QRISK3)	0.01713	0.01425 to 0.02002	0.03821	0.03544 to 0.04098	0.02679	0.02392 to 0.02966	0.02588	0.02281 to 0.02894	0.04828	0.04513 to 0.05143
Age^2 × male × logit (QRISK3)	−0.00016	−0.00021 to −0.00011	−0.00034	−0.00039 to −0.00030	−0.00027	−0.00032 to −0.00022	−0.00027	−0.00033 to −0.00022	−0.00040	−0.00046 to −0.00034

Note
QRISK3: 10-year QRISK3-predicted risk of CVD.

Repeating steps 1–3 for each other event gives:

$$P(\text{SA})_I = 5.29 \times P(\text{CV death})_I, P(\text{UA})_I = 1.60 \times P(\text{CV death})_I, P(\text{Stroke})_I = 1.97 \times P(\text{CV death})_I, P(\text{TIA})_I = 1.51 \times P(\text{CV death})_I. \quad (9)$$

People who had a cardiovascular event recorded in the CPRD data set must have had one of these types of events or be classified as a cardiovascular death. Therefore, the sum of these absolute probabilities, along with that of cardiovascular death, must equal 1:

$$P(\text{MI})_I + P(\text{SA})_I + P(\text{UA})_I + P(\text{Stroke})_I + P(\text{TIA})_I + P(\text{CV death})_I = 1. \quad (10)$$

Now, we can substitute the values from *Equation 7* into *Equation 8* and use the result to calculate the probability of the reference event: cardiovascular death:

$$3.22 \times P(\text{CV death})_I + 5.29 \times P(\text{CV death})_I + 1.60 \times P(\text{CV death})_I + 1.97 \times P(\text{CV death})_I + 1.51 \times P(\text{CV death})_I + P(\text{CV death})_I = 1 \leftrightarrow 14.59 \times P(\text{CV death})_I = 1 \leftrightarrow P(\text{CV death})_I = \frac{1}{14.59} = 0.07. \quad (11)$$

Finally, we compute the absolute probabilities of each event from *Equation 7* using the value we calculated for *P*(CV death)*I*:

$$P(\text{MI})_I = 0.22, P(\text{SA})_I = 0.36, P(\text{UA})_I = 0.11, P(\text{Stroke})_I = 0.14, P(\text{TIA})_I = 0.10. \quad (12)$$

Figure 36 illustrates the results of the model for men and women at a range of ages and underlying levels of cardiovascular risk. For comparison, *Figure 36* also shows the raw distribution of first events in the CPRD data to which we fitted the model. Strokes and cardiovascular deaths become more common first events as people get older. In contrast, the probability that the first sign of CVD will be an acute coronary event (MI or UA) is highest in younger people. Predicted cardiovascular risk at baseline and sex have relatively little influence on the distribution of events.

The events available in the CPRD data set comprise only events used by QRISK3 as predictors (i.e. SA, UA, MI, stroke, TIA and cardiovascular death). Therefore, we had to replicate the approach used in CG181 of combining predicted events within each cohort with external evidence estimating age- and sex-specific rates of PAD[169] and heart failure.[170]

To extend our example of a 50-year-old woman, this evidence suggests that, for women in the age bracket of 45–55 years, there are 6.3% as many cases of heart failure and 62.5% as many cases of PAD as QRISK3 events. This means that the QRISK3 events accounted for: $1/[P(\text{PAD})I + P(\text{HF})I + 1] = 0.593$. Multiplying this number by our calculations from *Equation 10* we arrive at our final proportions:

$$P(\text{MI})_I = 0.131, P(\text{SA})_I = 0.215, P(\text{UA})_I = 0.055, P(\text{Stroke})_I = 0.080, P(\text{TIA})_I = 0.061, P(\text{CV death})_I = 0.041, P(\text{PAD})_I = 0.370, P(\text{HF})_I = 0.037. \quad (13)$$

Health-related quality of life: underlying

We created the data set we used from a pooled sample of respondents from the HSE.[133] The HSE is a nationally representative cross-sectional sample of people residing privately in England. Each year, respondents complete a set of core questions about their general health (including the EQ-5D-3L), their lifestyle choices and behaviour, as well as their personal characteristics. From year to year, additional

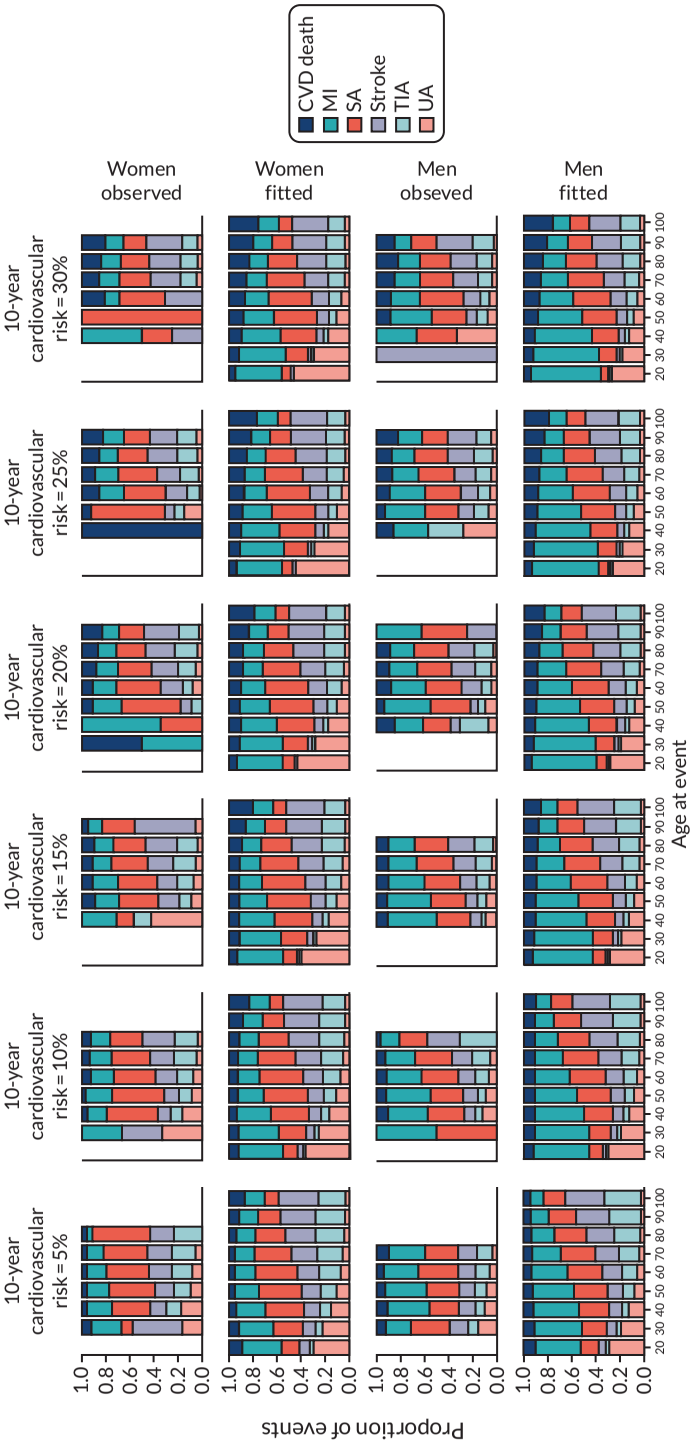

FIGURE 36 First CVD event stratified by age, sex and CVD risk: predictions from multinomial model compared with observed data from CPRD.

modules are integrated within the HSE and respondents are asked detailed questions about particular topics. We pooled HSE data sets from 2003, 2006 and 2011, as these surveys focused on CVD, with respondents being asked whether or not they had ever been specifically diagnosed with CVD by a doctor. After pooling the data, we dropped individuals with missing data for age and EQ-5D-3L. The remaining sample (n = 26,400) included only people who reported having no doctor-diagnosed CVD.

To account for non-linearity in the relationship between age and quality of life, we explored a range of polynomial forms. We introduced sex as a covariate and tested various degrees of interaction with the age terms. The model that best described the data (i.e. the most parsimonious model with AIC within 3 points of the lowest observed) had a quintic form with full interaction with sex (equivalent to fitting separate models for men and women). *Table 48* details the final model.

For people aged 90–100 years, we did not use modelled quality-of-life estimates and, instead, we relied on a simple average of values for men and women in that age group. We did this because data for nonagenarians are very scanty in the HSE data set (with only 52 women and 26 men represented) and, although it is clear that quality of life in the 10th decade is lower than in preceding years, there is no indication of a within-decade decline in this subpopulation of people with no cardiovascular history. Contrary to this, a continuous function fitted to all ages results in a dramatic drop-off in quality of life between 90 and 100 years (as the continuous function extrapolates the decline that is seen in the more plentiful data for previous decades). This can be solved by incorporating higher-order polynomial terms for age, but this results in implausible tail effects, where quality of life suddenly and markedly improves among the oldest people. We concluded that there are simply not enough data to assume any trends in within-decade quality of life for nonagenarians, and used a simple average instead (*Table 49*).

TABLE 48 Polynomial regression estimating quality of life in people aged 16–89 years with no history of CVD from HSE data

Parameter	EQ-5D-3L (95% CI)
Constant	1.0800 (0.8332 to 1.3268)
Male	0.2198 (−0.1610 to 0.6006)
Age	−0.0181 (−0.0496 to 0.0135)
Age^2	9.59×10^{-4} (-5.37×10^{-4} to 2.46×10^{-3})
Age^3	-2.57×10^{-5} (-5.89×10^{-5} to 7.60×10^{-6})
Age^4	3.11×10^{-7} (-3.81×10^{-8} to 6.60×10^{-7})
Age^5	-1.41×10^{-9} (-2.81×10^{-9} to -1.29×10^{-11})
Male × age	−0.0270 (−0.0759 to 0.0220)
Male × age^2	1.28×10^{-3} (-1.06×10^{-3} to 3.61×10^{-3})
Male × age^3	-2.85×10^{-5} (-8.07×10^{-5} to 2.37×10^{-5})
Male × age^4	3.07×10^{-7} (-2.45×10^{-7} to 8.59×10^{-7})
Male × age^5	-1.27×10^{-9} (-3.49×10^{-9} to 9.55×10^{-10})

TABLE 49 Quality of life in people aged ≥ 90 years with no history of CVD from HSE data[133]

Parameter	*n*	EQ-5D-3L (95% CI)
Women	52	0.638 (0.568 to 0.705)
Men	26	0.531 (0.381 to 0.679)

Figure 37 provides a visualisation of the new fitted model and alternative approaches compared with the underlying data. It is clear that the linear decline assumed in CG181 provides a poor approximation, as it overestimates quality of life in the oldest and youngest people and underestimates it for people aged 40–85 years. The quadratic function suggested by Ara and Brazier[156] provides a better fit, especially for women; however, it is less well suited to men, overestimating quality of life in the first three decades of adulthood and underestimating quality of life from age 60 to 90 years.

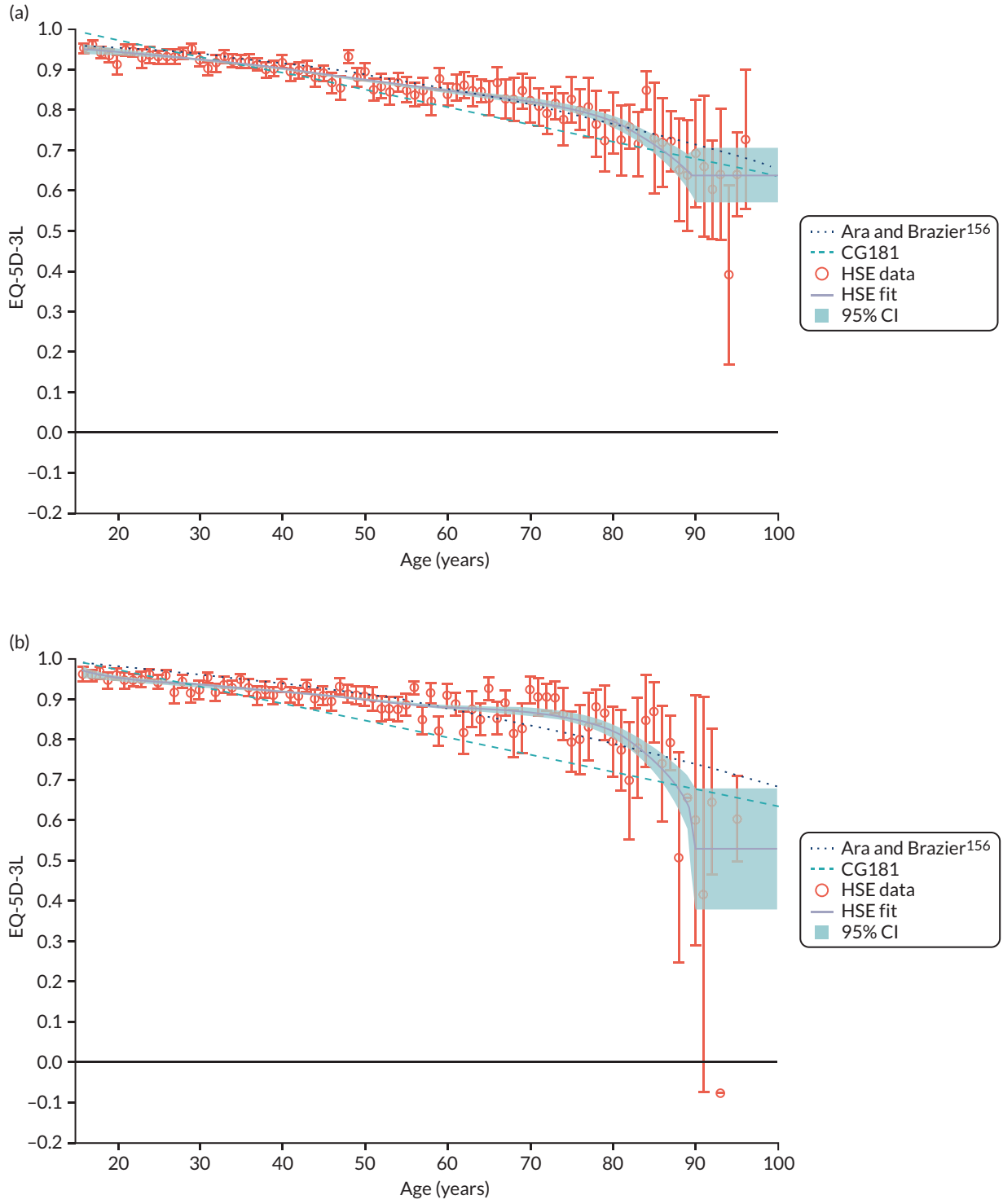

FIGURE 37 Underlying quality of life of people with no history of CVD: new polynomial model compared with linear assumption from CG181 and quadratic model from Ara and Brazier.[156] (a) Women; and (b) men.

For similar reasons, for women up until age 85 years, our new quintic model mirrors Ara and Brazier's[156] quadratic model fairly closely, but differences are more apparent in men. In particular, the raw data suggest that – in this subgroup of men with no cardiovascular history (which will become an increasingly atypical group as age rises) – quality of life is fairly well preserved throughout middle age, and only begins to tail off appreciably in their 80s and 90s. This suggests that a good proportion of the expected decline in the quality of life of men as they age can be attributed to CVD itself (or other morbidities that are strongly correlated with cardiovascular events). The remaining men with no cardiovascular history – the population of interest for our primary prevention decision problem – appear to escape without much deterioration in their underlying utility, and our new model captures this where other alternatives do not.

Health-related quality of life: cardiovascular events

To quality adjust expected survival for cost–utility analysis of a state-transition models, we require estimates of the quality of life associated with each of the model states. We updated the health state utility values from the CG181 model using a systematic review and in accordance with the Centre for Reviews and Dissemination guidelines.[171] To identify estimates for each model state, we adopted a pragmatic approach following recommendations in the NICE Decision Support Unit's technical support document for utility values.[134]

Table 50 reports the focus [i.e. population, intervention, comparator, outcome, study type (PICOS)] of this review. Two reviewers screened titles and abstracts for inclusion, resolving conflicts by consensus. Following this, one reviewer screened full texts for inclusion. A second reviewer checked a sample of full texts. One reviewer extracted data from the included studies. The protocol was published (PROSPERO CRD42021249959).[172]

We searched MEDLINE and EMBASE databases via Ovid. The search strategy combined cardiovascular terms from CG181 with the York precision-maximising filter for utility values.[173] We excluded studies if they were unavailable in English or used only condition-specific measures of quality of life.

TABLE 50 Focus of the review

Characteristic	Description
Population	Adult (aged ≥ 18 years) with one of the prespecified conditions of interest
Intervention	Experiencing a prespecified health state or condition: • SA • Post SA • UA • Post UA • MI • Post MI • TIA • Post TIA • Stroke • Post stroke • Heart failure • Post heart failure • Peripheral artery disease • Post peripheral artery disease
Comparator	Utility value for an adult population without the specified health states or conditions of interest
Outcome	Mean utility score with measure of dispersion
Study type	Empirical study using direct or indirect measurement methods to produce utility values

The search returned 5080 distinct studies, of which 4132 were excluded on abstract screening (*Figure 38*). A further 526 studies were excluded on full-text screening for the following reasons: 165 studies had no primary data; 128 studies did not consider any of our specified health states; 32 studies considered unrepresentative subgroups of specified states only; 2 studies collected only condition-specific measures of health-related quality of life; 157 studies did not report overall health-related quality-of-life estimate; and 44 studies were unavailable to download or were unavailable in English.

The review results included studies that collected EQ-5D-3L responses from British populations with each of the specified conditions, with the exception of PAD. Estimates based on European EQ-5D-3L responses, evaluated according to the British tariff, were available for PAD. For each of the events that had an associated post-event state, it was possible to source HSUVs for post-event states from the same source as first year.

We filtered the results of the review to show studies that evaluated the EQ-5D-3L responses of British, or similar, populations according to a UK tariff. We assessed the relevance of these studies to our purposes using high-level characteristics, such as sample size and the number of conditions of interest considered. We identified the studies judged to be most suitable as candidates from which to source disutility multipliers for the model. We used a self-developed quality assessment tool to compare candidate studies according to risk of bias and applicability. There were nine candidate studies in total.[174–182]

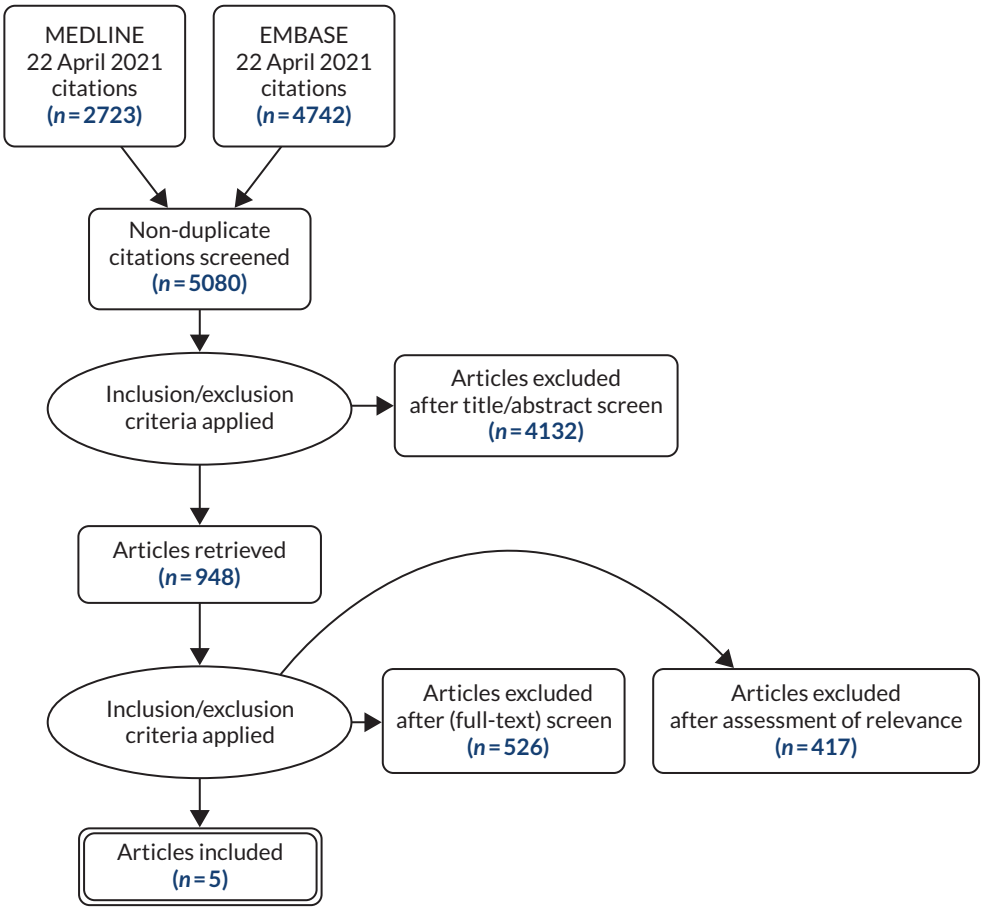

FIGURE 38 A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart for systematic review of health state utility values.

A set of disutilities for the health states of interest was chosen according to their critical appraisal performance and clinical face validity when compared with one another. Two clinicians assessed the face validity of the chosen set of disutilities. The two clinicians confirmed that each estimate, as well as the rank order between them, was plausible.

We selected a study recruiting people experiencing their first TIA (*n* = 314) or stroke (*n* = 445) across five general practices.[174] Heart failure estimates were sourced from cases (*n* = 260) detected from clinics/acute care/GPs at two UK sites in 2006–8.[176] For SA, we pooled results across three management strategies for people aged ≥ 30 years with suspected SA who were suitable for revascularisation.[182] For PAD, we used data from 204 consecutive cases of PAD diagnosed by ankle-brachial index of ≤ 0.9 in the Netherlands, evaluated using UK tariff.[180]

If we were to choose our preferred sources for each individual state independently, there is a risk that we would be left with an implausible ranking of multipliers. For MI, it appeared that a study covering all UK cases in a 5-year period[181] was the best source based on critical appraisal and recruitment policy. However, when chosen together with our preferred source for SA,[182] the study suggested that angina decreases health-related quality of life to a greater extent than MI. To avoid an implausible ordering of these states, we chose a third study (which considered multiple states of interest, but considered only three sites rather than the whole UK) for both UA (*n* = 898) and MI (*n* = 1176).[179] People who were aged ≥ 18 years and who had not been revascularised or received a coronary artery bypass graft within the previous 6 months were eligible for inclusion in this study. We did not use separate values for any comorbidities of the conditions modelled. We did not use three of the candidate studies[175,177,178] identified by the review.

Three of the source studies[174,179,182] had the advantage of being longitudinal. We calculated average annual utility from the time points given using the AUROC approach. Otherwise, the single estimates provided were used.[176,180] The studies used for stroke, TIA and MI provided estimates of quality of life 1 month after the event in question, but did not give a baseline value.[174,179] For stroke and TIA, our area under the curve calculations assumed that baseline values were equal to those at 1 month. For MI, we applied the ratio of baseline to 1-month estimates from an alternative source[181] to the 1-month estimates from the study used to derive a baseline estimate.

We applied utility values to baseline quality of life using a multiplicative approach. For stroke and TIA, the study reported health-related quality of life of controls without CVD[174] and so we used this directly to estimate the relative impact of the events. For other states, we calculated disutility multipliers by comparing reported EQ-5D-3L values with our prediction of baseline utility for people with the same mean age and proportion of men and women but no CVD (see above). The model multiplies the age- and sex-specific baseline utility by the relevant disutility multiplier to adjust people's quality of life accordingly (*Table 51*).

Resource use and costs: cardiovascular events

We performed a rapid review using pearl-growing from two previously known sources: one for stroke/TIA[140] and one for cardiovascular events.[141] *Table 52* reports the focus (PICOS) of this review. One researcher conducted the pearl-growing and checked citations of included studies. For the rapid review, the researcher used the medical subject heading terms for the original pearl papers to find similar papers in both MEDLINE and EMBASE using Ovid Online. These papers were combined with the papers found using the 'Find Similar' tool within Ovid Online. Finally, all references within the pearls were extracted and combined with any papers citing the pearls. The researcher then removed duplicates and screened titles and abstracts of studies identified for inclusion based on PICOS. Following this, two researchers screened full texts for inclusion based on PICOS. One researcher extracted data from the included studies and a second researcher checked the extraction.

TABLE 51 Disutility multipliers used in the model (base case)

Health state	EQ-5D-3L disutility multiplier (95% CI)[a]	Risk of bias	Relevance	Source	CG18115
SA	0.865 (0.852 to 0.876)	Minor	Direct	Walker *et al.*[182]	0.808
Post SA	0.869 (0.854 to 0.883)				
UA	0.740 (0.719 to 0.762)	Minor	Direct	Pockett *et al.*[179]	0.770
Post UA	0.731 (0.711 to 0.752)				0.880
MI	0.816 (0.800 to 0.833)	Minor	Direct	Pockett *et al.*[179]	0.760
Post MI	0.818 (0.800 to 0.837)				0.880
TIA	0.899 (0.871 to 0.927)	Minor	Direct	Luengo-Fernandez *et al.*[174]	0.900
Post TIA	0.892 (0.862 to 0.924)				
Stroke	0.808 (0.784 to 0.834)	Minor	Direct	Luengo-Fernandez *et al.*[174]	0.628
Post stroke	0.788 (0.757 to 0.819)				
Heart failure	0.714 (0.671 to 0.754)	Minor	Direct	Mejía *et al.*[176]	0.683
Post heart failure					
PAD	0.756 (0.722 to 0.792)	Minor	Partial	Vaidya *et al.*[180]	0.808
Post PAD					

a CI calculated by simulation in model, accounting for uncertainty in multiple input parameters (e.g. multiple time points in area under the curve calculations).

TABLE 52 Focus of the review

Characteristic	Description
Population	Adult (≥ 18 years) with one of the prespecified conditions of interest
Intervention	Experiencing a prespecified health state or condition: • SA • Post SA • UA • Post UA • MI • Post MI • TIA • Post TIA • Stroke • Post stroke • Heart failure • Post heart failure • PAD • Post PAD
Comparator	NHS costs for an adult population without the specified health states or conditions of interest
Outcome	Mean cost with measure of dispersion
Study type	Empirical study or review reporting cost data

We included five studies[140,141,182–184] and used the studies to select a set of base-case values (*Table 53*).

We required annual costs in both the year of the event and following years (i.e. post event). When possible, we chose studies reporting values in a format that most closely reflected first-year and post-event costs for the base case. We sought to source the post-event costs from the same studies as the year 1 costs.

Furthermore, we required incremental costs compared with healthcare costs for somebody in the primary prevention population and, therefore, we chose studies reporting incremental costs for the base case where possible. When we deemed estimates to be equally relevant, we chose those with more recent cost-years for the base case. All cost-years were projected to 2019–20, which was the year for which the most recent inflators[163] and Personal Social Services Research Unit costs of health and social care[159] were available at the time of analysis.

We discounted estimated social care costs of stroke and post-stroke by 50% to reflect the proportion of this cost that we assume is paid out-of-pocket by individuals (this assumption has precedent in NICE guidelines[185–187]). In the source study,[140] disaggregated health and social care costs were available for only all strokes and not for ischaemic stroke, which we preferred for our decision context. Therefore, we approximated the required numbers by applying the ratio of overall ischaemic stroke costs to overall all stroke costs to disaggregated health and social care costs for all strokes.

TABLE 53 Studies included in the rapid review of health-state costs

Health state	Cost (£), mean (95% CI)[a]	Source	Original cost-year	Note	CG181[10] cost (£)	
					Original	Inflated
SA	1592 (1445 to 1734)	Walker *et al.*[182]	2016–7	Pooled across trial arms	7736	8700
Post SA	130 (105 to 158)				240	270
UA	2591 (2473 to 2717)	Danese *et al.*[141]	2013–4		3314	3727
Post UA	363 (227 to 501)				385	433
MI	5238 (4951 to 5511)	Danese *et al.*[141]	2013–4		3337	3753
Post MI	1020 (667 to 1365)				788	886
TIA	2089 (1882 to 2305)	Danese *et al.*[141]	2013–4		578	650
Post TIA	779 (481 to 1092)				124	139
Stroke	17,528 (16,639 to 18,494)	Xu *et al.*[140]	2015–6	Ischaemic stroke only; assumes that 50% of social care costs are met by the individual	4092	4602
Post stroke	3459 (3058 to 3824)				155	175
HF	3171 (2842 to 3507)	Danese *et al.*[141]	2013–4		2297	2583
Post HF	937 (391 to 1489)				2597	2921
PAD	1888 (1739 to 2040)	Walker *et al.*[184]	2011–2	CVD costs only; estimate for 'history of PAD' assumed for in-year and post-PAD	952	1070
Post PAD					529	595
CV death	2306 (2250 to 2362)	Walker *et al.*[184]	2011–2	All healthcare costs	1174	1320
Non CV death	2572 (2528 to 2615)				0	0

CV, cardiovascular; HF, heart failure.
a CI calculated by simulation in model, in most cases accounting for uncertainty in multiple input parameters.

One study[184] reported a regression model to calculate costs depending on characteristics, such as age and sex. Therefore, we adjusted costs from this study for start age and sex of each cohort modelled. The average cost reported in each other study was applied to all cohorts.

Two studies[141,184] included reported estimates for multiple model states. In the base case, we prioritised choosing the most relevant estimates for each state over consistently sourcing from the same paper, and this meant that we used a combination of estimates from the two studies.[141,184] We did, however, model scenarios that relied on each of the two studies wherever possible and used base-case values otherwise. In one of these scenarios, reported model coefficients were applied to costs for SA to calculate costs for other states because people with SA were the reference population for the source study.[184] In a final two scenarios, we used the values from CG181 in its original cost-year and then inflated to 2019–20.

Formal specification of relative survival model

We used the multiplicative version of the relative survival model from formula 6 of Andersen *et al.*[142] to predict the effect of cardiovascular risk on time of non-cardiovascular death. Let the adjusted hazard of non-cardiovascular death be given by $\lambda_{unadj.}$. Therefore, as in *Equation 12* of Pohar and Stare,[188] the adjusted hazard, $\lambda_{adj.}$, for covariate values $[x_1,..., x_k]d$ and coefficients $[\beta_0, \beta_1,..., \beta_k]$, is given by:

$$\lambda_{adj.} = \lambda_{unadj.} \times e^{\beta_0+\beta_1 x_1+\ldots+\beta_k x_k}. \quad (14)$$

We can express $\lambda_{unadj.}$ as the exponent of its own natural logarithm. Therefore, the above is equivalent to:

$$\lambda_{adj.} = e^{\ln(\lambda_{unadj.})} \times e^{\beta_0+\beta_1 x_1+\ldots+\beta_k x_k}. \quad (15)$$

Then, applying the laws of multiplication for exponents, we obtain:

$$\lambda_{adj.} = e^{\ln(\lambda_{unadj.})+\beta_0+\beta_1 x_1+\ldots+\beta_k x_k}. \quad (16)$$

This can be interpreted in the same way as a Cox model with a log-transformed unadjusted hazard of survival included as a covariate and with coefficient β_f fixed at 1:

$$\lambda_{adj.} = e^{\beta_0+\beta_1 x_1+\ldots+\beta_k x_k+\beta_f \ln(\lambda_{unadj.})}. \quad (17)$$

Accounting for competing risk of non-cardiovascular death

As explained in the main text, the critical covariate for our relative survival models is Δlogit(*Q*), that is the difference between an individual's predicted 10-year QRISK3 score and the average score for a person of the same age and sex. We estimate the latter using a regression on the CPRD data set. *Table 54* shows the model coefficients and *Figure 39* shows the model fitted for men and women as a function of age. We found that the relationship between age and logit(QRISK3) was best described by a quintic function. Although still-higher-order polynomials reduced measures of model fit (AIC) further, we observed that their introduction caused artefacts at high ages (e.g. a sudden reduction in expected risk) that strongly suggested overfitting. Therefore, we preferred the quintic model.

TABLE 54 Regression estimating population average logit(QRISK3 10-year cardiovascular risk) as a function of sex and age

Parameter	Estimate (95% CI)
Intercept	−12.90 (−13.21 to −12.58)
Age	0.353 (0.319 to 0.387)
Age^2	-5.60×10^{-3} (-6.99×10^{-3} to -4.21×10^{-3})
Age^3	6.31×10^{-5} (3.54×10^{-5} to 9.08×10^{-5})
Age^4	-4.18×10^{-7} (-6.85×10^{-7} to -1.51×10^{-7})
Age^5	1.42×10^{-9} (4.29×10^{-10} to 2.42×10^{-9})
Male	−11.02 (−11.48 to −10.55)
Male × age	0.986 (0.936 to 1.036)
Male × age^2	0.0320 (−0.0341 to −0.0300)
Male × age^3	5.20×10^{-4} (4.79×10^{-4} to 5.61×10^{-4})
Male × age^4	-4.28×10^{-6} (-4.68×10^{-6} to -3.88×10^{-6})
Male × age^5	1.41×10^{-8} (1.26×10^{-8} to 1.56×10^{-8})

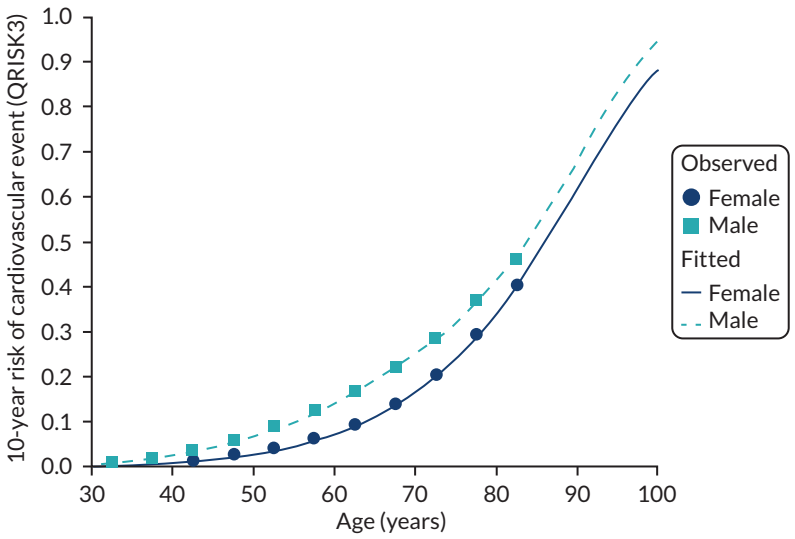

FIGURE 39 Average 10-year risk of cardiovascular event (QRISK3) in people with no history of CVD as a function of age and sex.

Appendix 7 Full results from updated cost–utility model assessing statins for the primary prevention of cardiovascular disease before accounting for competing risk and direct treatment disutility

This appendix contains cost–utility results from the statins model following the updates described in *Chapter 6*, *General model updates*, that is the model includes all the steps we took to update and enhance the CG181 model but does not account for competing risk or DTD.

Base case

Deterministic incremental cost–utility results

Table 55 replicates the structure of Table 97 in appendix L of CG181,[10] showing estimated costs and QALYs for each statin strategy and no treatment. *Figure 40* shows the option with greatest net benefit (when we value QALYs at £20,000 each) for men and women across a range of ages and levels of cardiovascular risk. *Table 55* also gives net health benefit (NHB) for each arm (valuing QALYs at £20,000 each).

TABLE 55 Updated CG181 model[10] (not accounting for competing risk or DTD): cost–utility results in men and women at various levels of non-cardiovascular risk

	60-year-old men			60-year-old women		
Strategy	**Cost (£)**	**QALY**	**NHB**	**Cost (£)**	**QALY**	**NHB**
10-year cardiovascular risk = 30%						
No statins	11,198	11.360	10.800	11,845	11.158	10.566
Low-intensity statin (S10)	11,423	11.622	11.051	12,052	11.438	10.836
Medium-intensity statin (S20)	10,653	11.796	11.263	11,248	11.628	11.065
High-intensity statin (A20)	10,686	11.949	11.415	11,291	11.796	11.231
High-intensity statin (A80)	10,772	11.949	11.410	11,379	11.796	11.227
10-year cardiovascular risk = 25%						
No statins	10,269	11.684	11.171	10,873	11.501	10.958
Low-intensity statin (S10)	10,606	11.927	11.396	11,191	11.763	11.203
Medium-intensity statin (S20)	9875	12.089	11.596	10,420	11.942	11.421
High-intensity statin (A20)	9892	12.226	11.731	10,443	12.092	11.570
High-intensity statin (A80)	9984	12.226	11.726	10,537	12.092	11.565

continued

TABLE 55 Updated CG181 model[10] (not accounting for competing risk or DTD): cost–utility results in men and women at various levels of non-cardiovascular risk (*continued*)

Strategy	60-year-old men			60-year-old women		
	Cost (£)	QALY	NHB	Cost (£)	QALY	NHB
10-year cardiovascular risk = 20%						
No statins	9183	12.030	11.571	9715	11.873	11.388
Low-intensity statin (S10)	9664	12.247	11.763	10,180	12.109	11.600
Medium-intensity statin (S20)	8989	12.393	11.944	9460	12.272	11.799
High-intensity statin (A20)	8994	12.509	12.060	9466	12.401	11.928
High-intensity statin (A80)	9091	12.509	12.055	9567	12.401	11.923
10-year cardiovascular risk = 15%						
No statins	7897	12.403	12.008	8311	12.280	11.865
Low-intensity statin (S10)	8564	12.585	12.157	8972	12.481	12.032
Medium-intensity statin (S20)	7967	12.709	12.311	8332	12.620	12.204
High-intensity statin (A20)	7966	12.802	12.404	8327	12.724	12.307
High-intensity statin (A80)	8069	12.802	12.398	8435	12.724	12.302
10-year cardiovascular risk = 10%						
No statins	6343	12.805	12.488	6567	12.730	12.402
Low-intensity statin (S10)	7258	12.944	12.581	7501	12.883	12.508
Medium-intensity statin (S20)	6773	13.039	12.700	6982	12.989	12.640
High-intensity statin (A20)	6774	13.104	12.766	6976	13.063	12.714
High-intensity statin (A80)	6883	13.104	12.760	7090	13.063	12.709
10-year cardiovascular risk = 9%						
No statins	5992	12.890	12.591	6165	12.826	12.518
Low-intensity statin (S10)	6965	13.018	12.670	7166	12.967	12.609
Medium-intensity statin (S20)	6509	13.107	12.781	6679	13.066	12.732
High-intensity statin (A20)	6511	13.166	12.841	6674	13.133	12.799
High-intensity statin (A80)	6622	13.166	12.835	6790	13.133	12.794
10-year cardiovascular risk = 8%						
No statins	5624	12.976	12.695	5742	12.924	12.637
Low-intensity statin (S10)	6661	13.093	12.760	6816	13.053	12.712
Medium-intensity statin (S20)	6236	13.175	12.863	6363	13.144	12.825
High-intensity statin (A20)	6240	13.228	12.916	6360	13.204	12.886
High-intensity statin (A80)	6352	13.228	12.911	6478	13.204	12.880
10-year cardiovascular risk = 7%						
No statins	5240	13.064	12.802	5296	13.024	12.759
Low-intensity statin (S10)	6345	13.170	12.852	6449	13.140	12.818
Medium-intensity statin (S20)	5952	13.243	12.946	6033	13.222	12.920
High-intensity statin (A20)	5958	13.291	12.993	6033	13.275	12.974
High-intensity statin (A80)	6072	13.291	12.987	6152	13.275	12.968

TABLE 55 Updated CG181 model[10] (not accounting for competing risk or DTD): cost–utility results in men and women at various levels of non-cardiovascular risk (*continued*)

Strategy	60-year-old men			60-year-old women		
	Cost (£)	QALY	NHB	Cost (£)	QALY	NHB
10-year cardiovascular risk = 6%						
No statins	4837	13.153	12.911	4825	13.126	12.885
Low-intensity statin (S10)	6015	13.247	12.946	6063	13.229	12.926
Medium-intensity statin (S20)	5657	13.313	13.030	5689	13.301	13.017
High-intensity statin (A20)	5667	13.354	13.071	5692	13.347	13.063
High-intensity statin (A80)	5781	13.354	13.065	5813	13.347	13.057
10-year cardiovascular risk = 5%						
No statins	4415	13.243	13.023	4327	13.230	13.014
Low-intensity statin (S10)	5670	13.325	13.042	5657	13.319	13.036
Medium-intensity statin (S20)	5350	13.382	13.115	5329	13.382	13.115
High-intensity statin (A20)	5364	13.417	13.149	5335	13.420	13.154
High-intensity statin (A80)	5480	13.417	13.143	5458	13.420	13.147

A20, Atorvastatin (20 mg/day); A80, atorvastatin (80 mg/day); S20, simvastatin (20 mg/day).

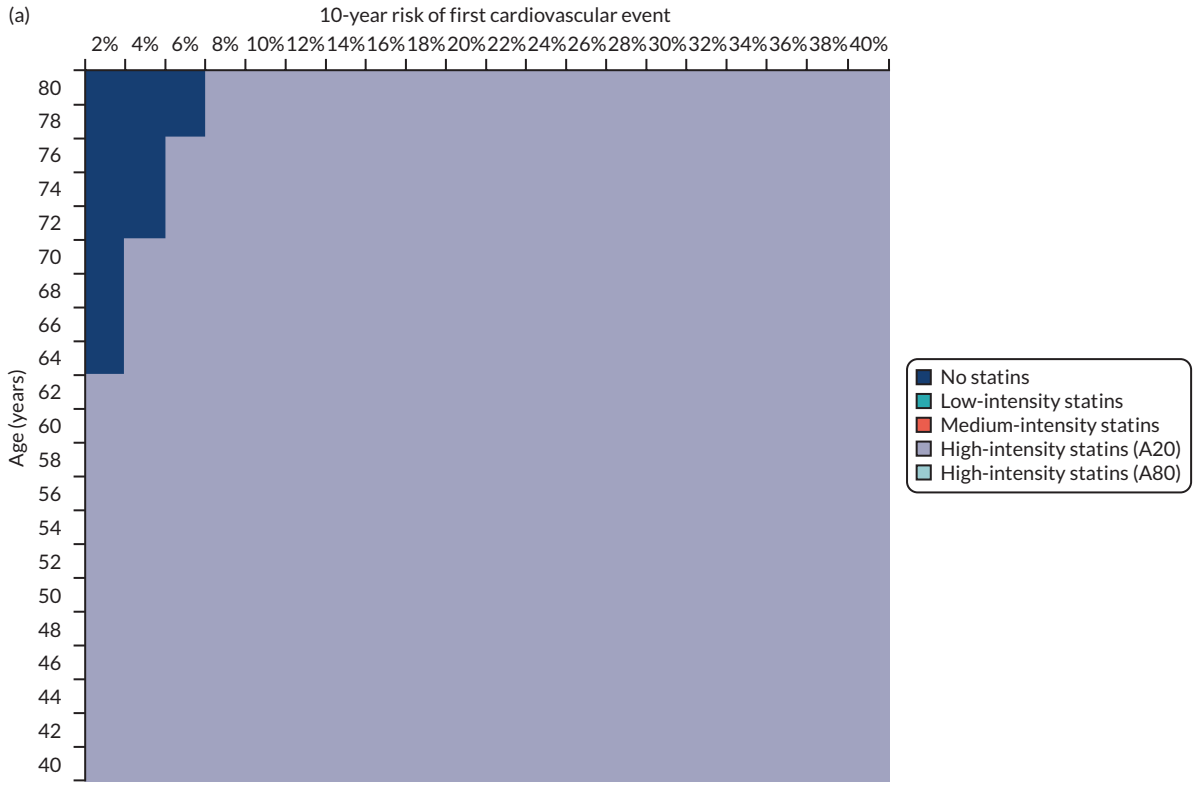

FIGURE 40 Updated CG181 model[10] (not accounting for competing risk or DTD): relationship between age and risk of non-cardiovascular death: cost-effectiveness of statins. (a) Men; and (b) women. Coloured area identifies option with highest net benefit when we value QALYs at £20,000 each. (*continued*)

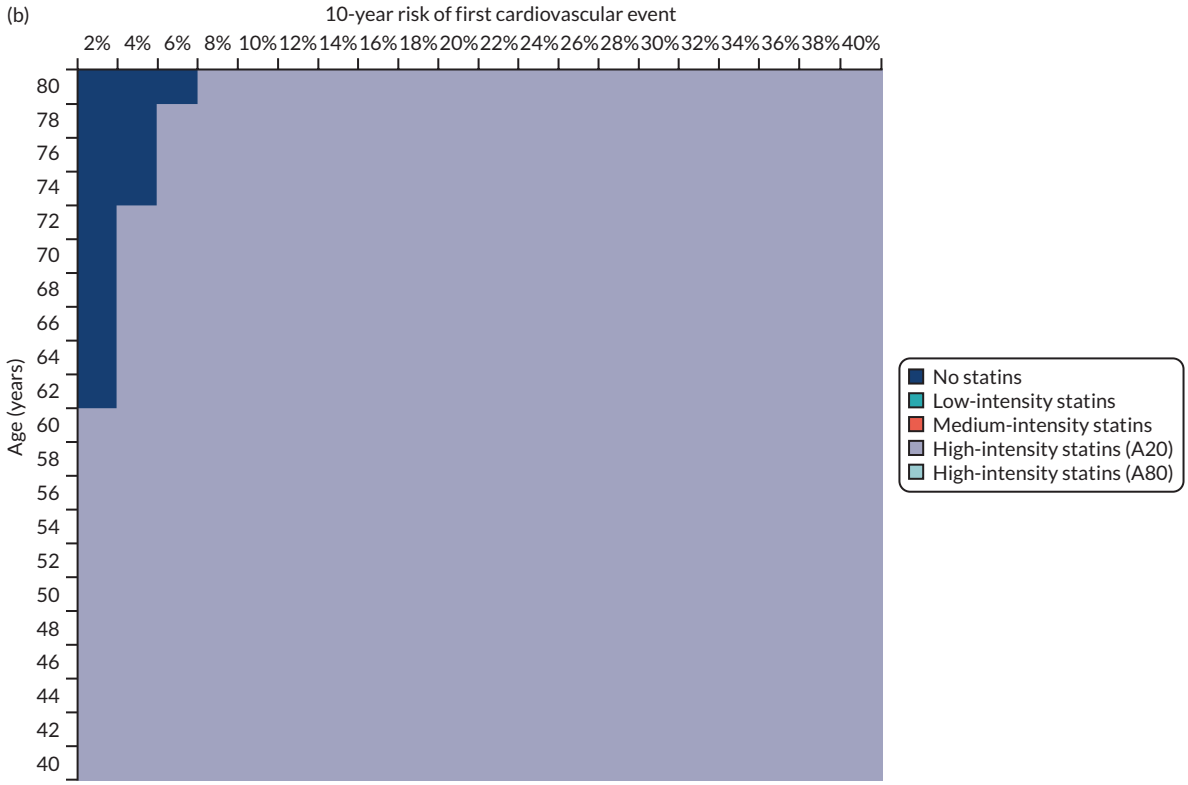

FIGURE 40 Updated CG181 model[10] (not accounting for competing risk or DTD): relationship between age and risk of non-cardiovascular death: cost-effectiveness of statins. (a) Men; and (b) women. Coloured area identifies option with highest net benefit when we value QALYs at £20,000 each.

Deterministic sensitivity analysis

One-way sensitivity analysis

One-way sensitivity analyses are depicted in *Figures 41–43*.

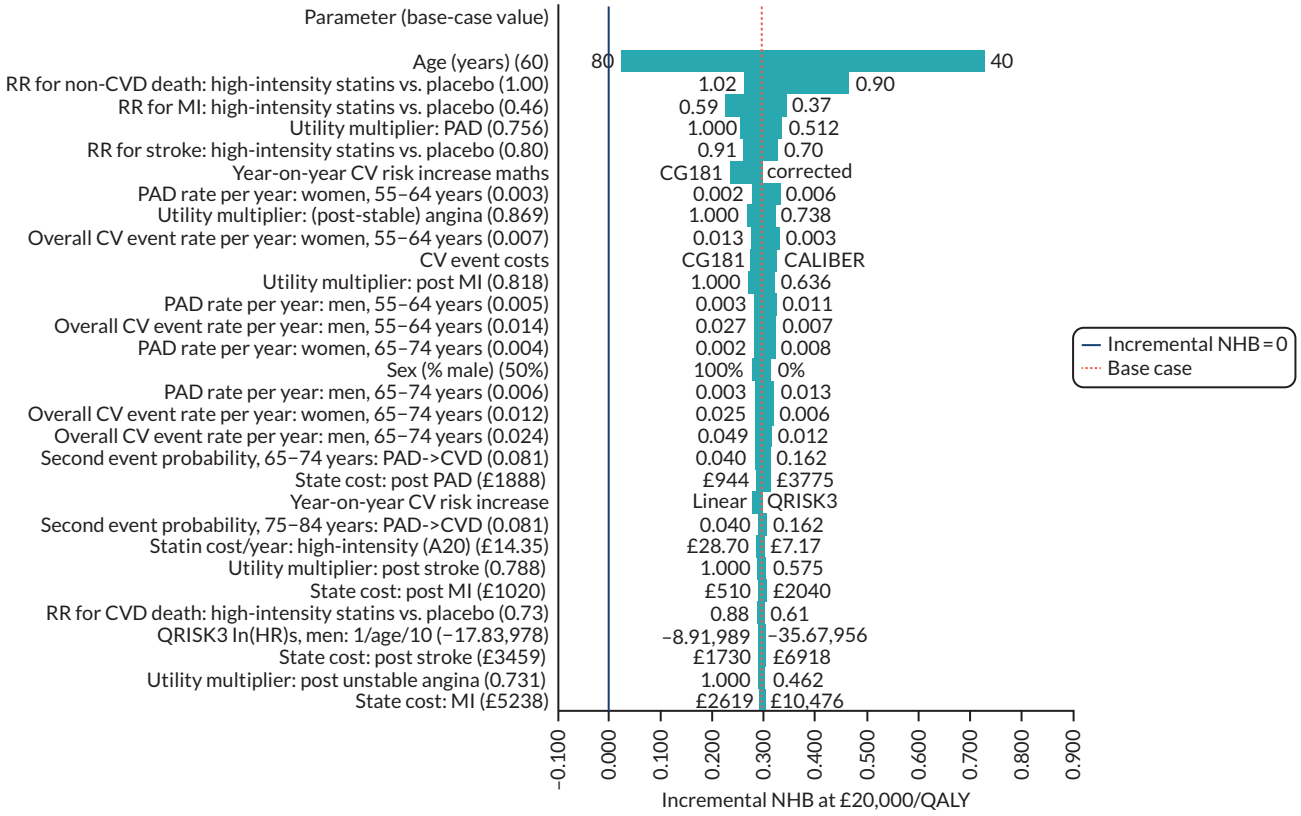

FIGURE 41 Updated CG181 model[10] (not accounting for competing risk or DTD): one-way sensitivity analysis for high-intensity statins (atorvastatin 20 mg/day) compared with no treatment. Thirty most influential parameters shown. Positive incremental NHB implies that high-intensity statins is the preferred option (i.e. it would be associated with an ICER of £20,000/QALY or better vs. no treatment). CV, cardiovascular; RR, relative risk.

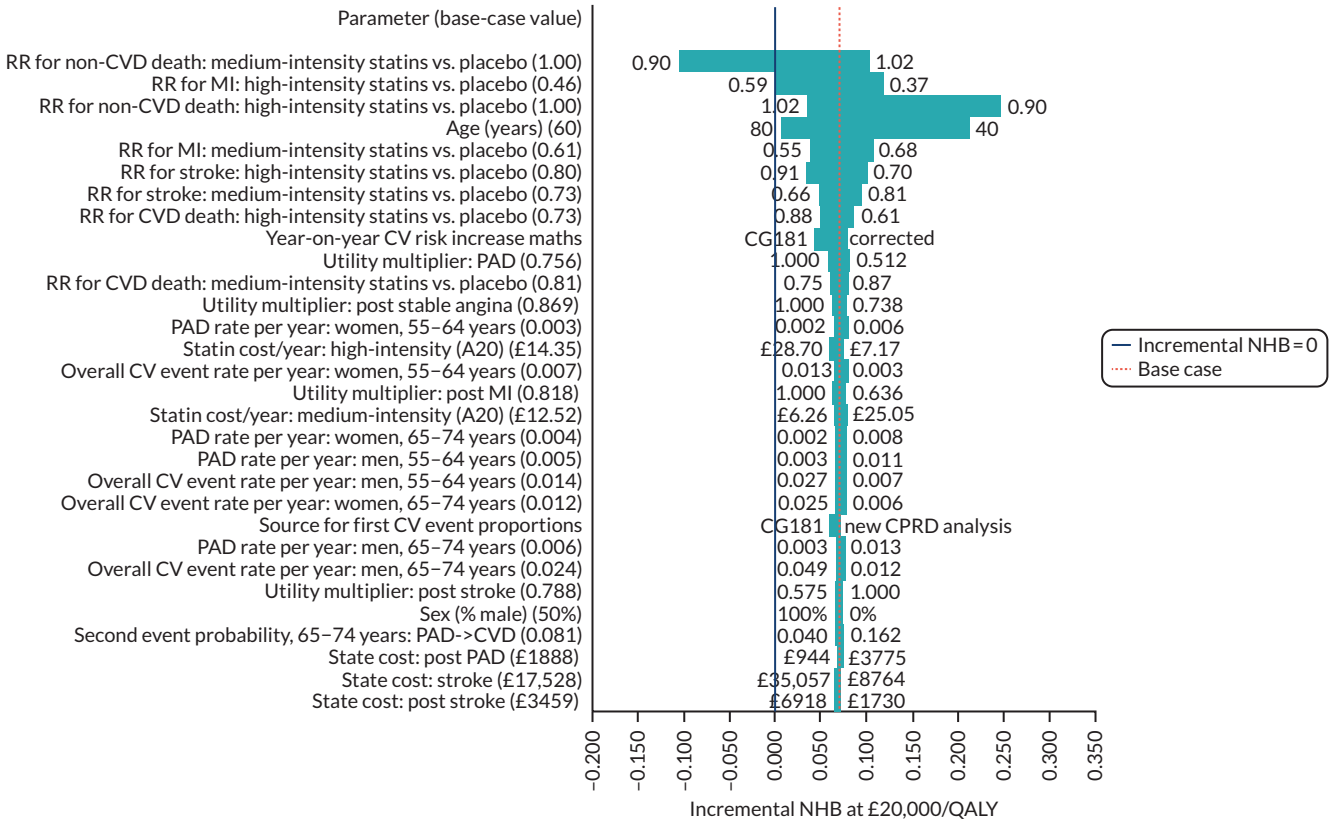

FIGURE 42 Updated CG181 model[10] (not accounting for competing risk or DTD): one-way sensitivity analysis for high-intensity statins (atorvastatin 20 mg/day) compared with medium-intensity statins (simvastatin 20 mg/day). Thirty most influential parameters shown. Positive incremental NHB implies that high-intensity statins is the preferred option (i.e. it would be associated with an ICER of £20,000/QALY or better vs. medium-intensity statins). CV, cardiovascular; RR, relative risk.

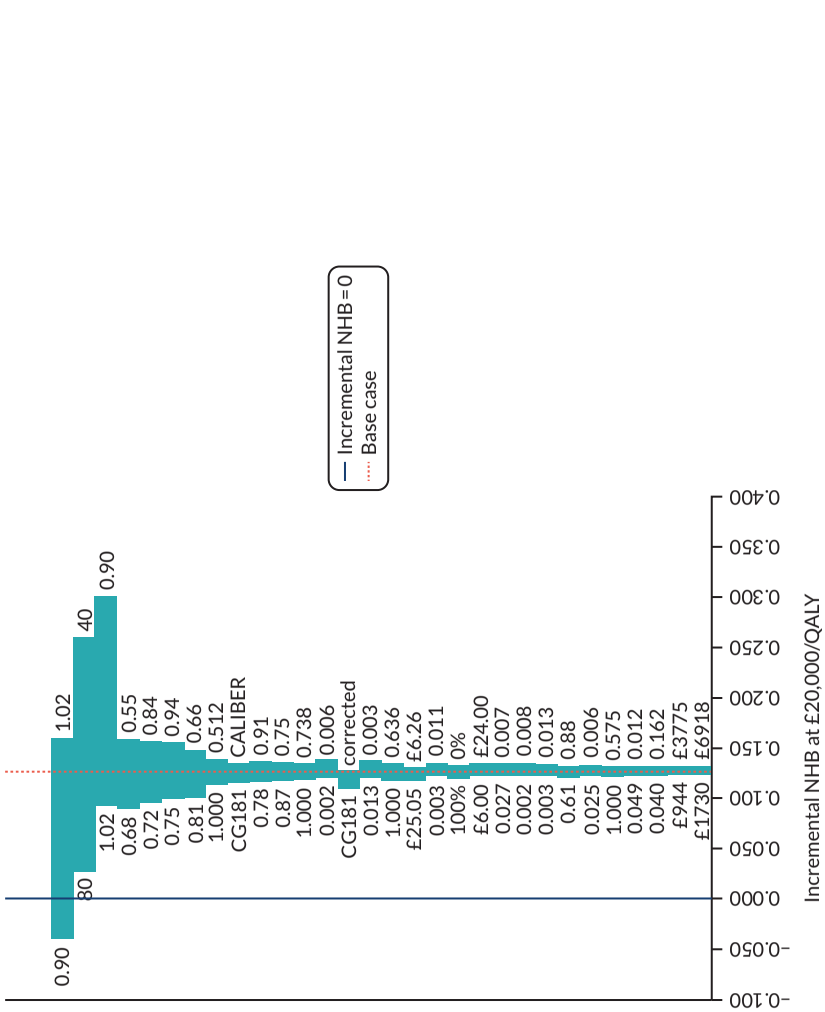

FIGURE 43 Updated CG181 model[10] (not accounting for competing risk or DTD): one-way sensitivity analysis for medium-intensity statins (simvastatin 20 mg/day) compared with low-intensity statins (simvastatin 10 mg/day). Thirty most influential parameters shown. Positive incremental NHB implies that medium-intensity statins is the preferred option (i.e. it would be associated with an ICER of £20,000/QALY or better vs. low-intensity statins). CV, cardiovascular; RR, relative risk.

Probabilistic sensitivity analysis

Probabilistic sensitivity analyses are depicted in *Figures 44–46*.

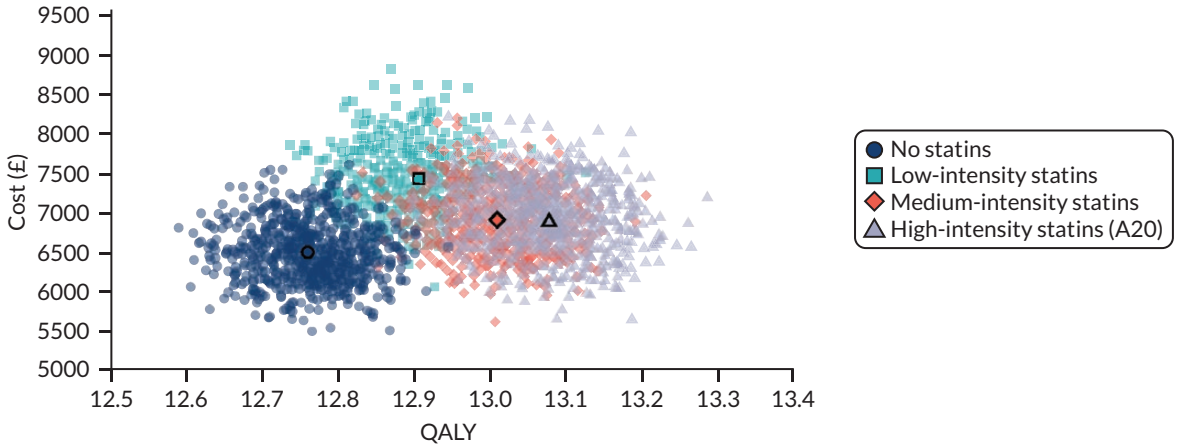

FIGURE 44 Updated CG181 model[10] (not accounting for competing risk or DTD): probabilistic cost–utility scatterplot for all options (60-year-olds; 50 : 50 men : women; 10-year risk of cardiovascular event = 10%).

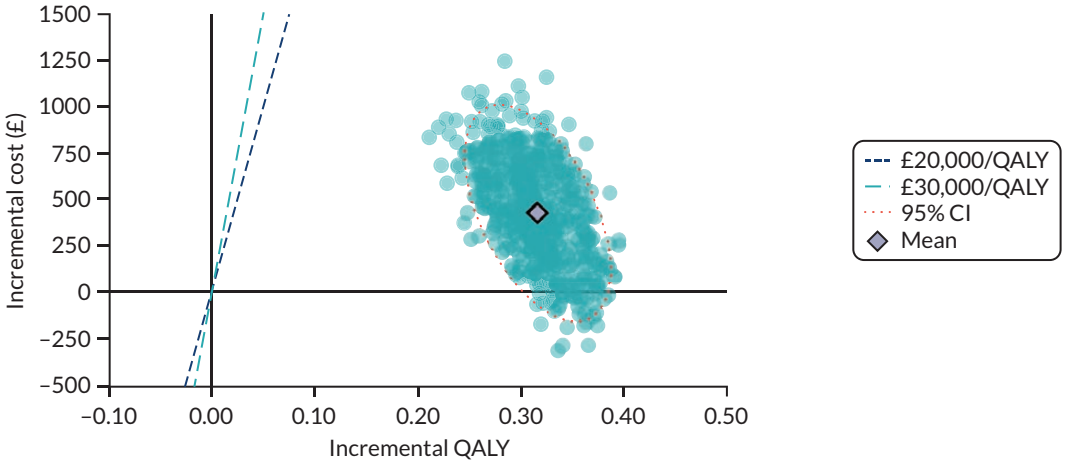

FIGURE 45 Updated CG181 model[10] (not accounting for competing risk or DTD): probabilistic incremental cost–utility scatterplot – high-intensity statins (atorvastatin 20 mg/day) compared with no treatment (60-year-olds, 50 : 50 men : women; 10-year risk of cardiovascular event = 10%).

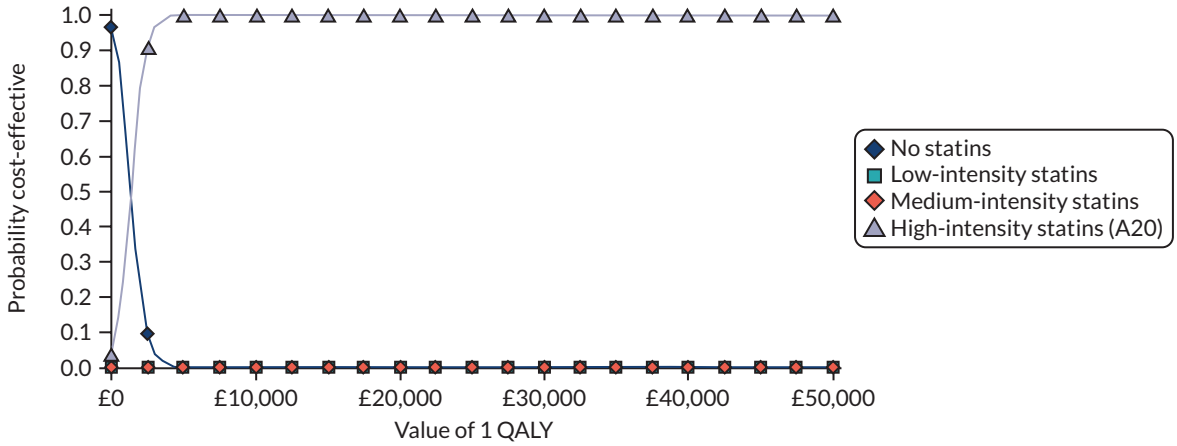

FIGURE 46 Updated CG181 model (not accounting for competing risk or DTD): cost-effectiveness acceptability curve (60-year-olds, 50 : 50 men : women; 10-year risk of cardiovascular event = 10%). Bold line shows cost-effectiveness acceptability frontier.

Appendix 8 Full results from cost–utility model assessing statins for the primary prevention of cardiovascular disease including adjustment for competing risk

This appendix contains cost–utility results from the statins model following the updates described in *Chapter 6*, *General model updates*, and subsequent inclusion of adjustment competing risk of non-cardiovascular death, as described in *Chapter 6*, *New model features specific to this project*.

Base case

State occupancy

Figure 47 provides model state occupancy graphs in two untreated cohorts with and without adjustment for competing risk of non-cardiovascular mortality. Both groups comprise 60-year-olds with a 10-year QRISK3-predicted risk of 10%, but one cohort is 100% male and the other cohort is 100% female.

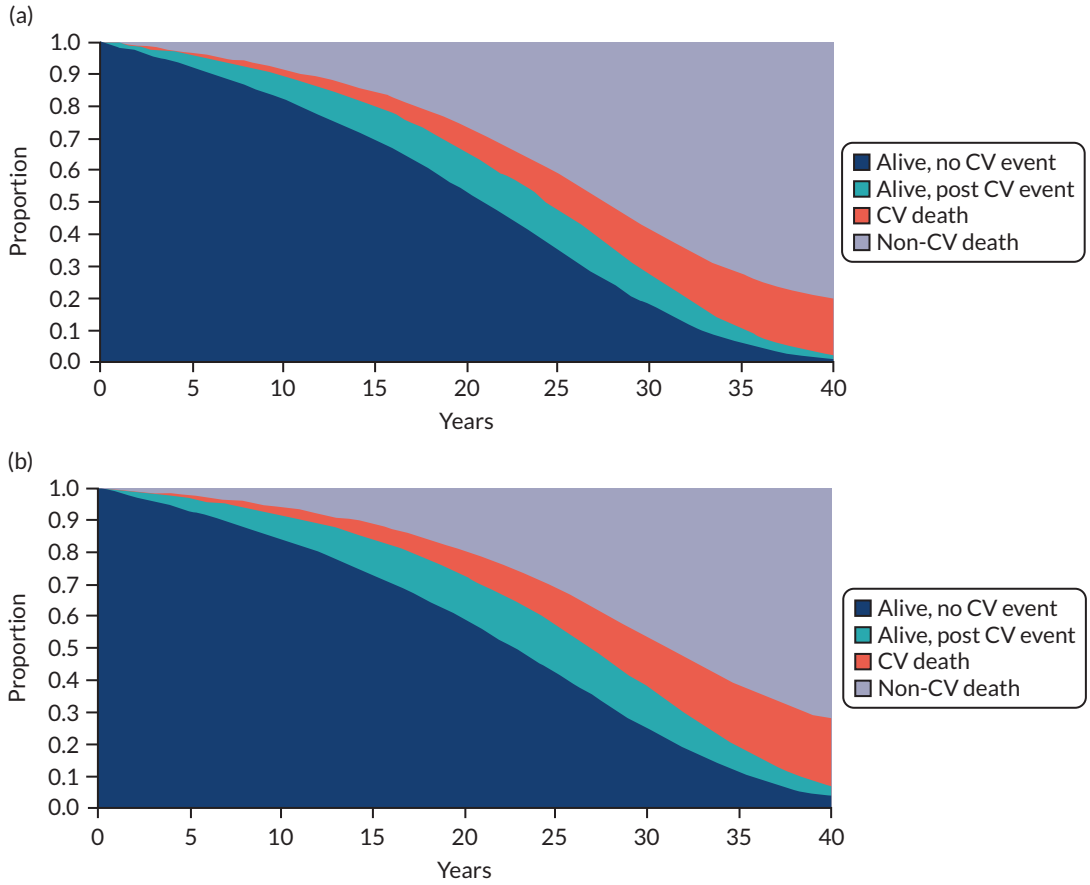

FIGURE 47 State occupancy (no treatment) with and without adjustment for competing risk of non-cardiovascular mortality in example cohorts. (a) 60-year-old men, 10-year cardiovascular risk=10%: unadjusted for competing risk of non-cardiovascular mortality; (b) 60-year-old women, 10-year cardiovascular risk=10%: unadjusted for competing risk of non-cardiovascular mortality; (c) 60-year-old men, 10-year cardiovascular risk=10%: adjusted for competing risk of non-cardiovascular mortality; and (d) 60-year-old women, 10-year cardiovascular risk=10%: adjusted for competing risk of non-cardiovascular mortality. CV, cardiovascular. (*continued*)

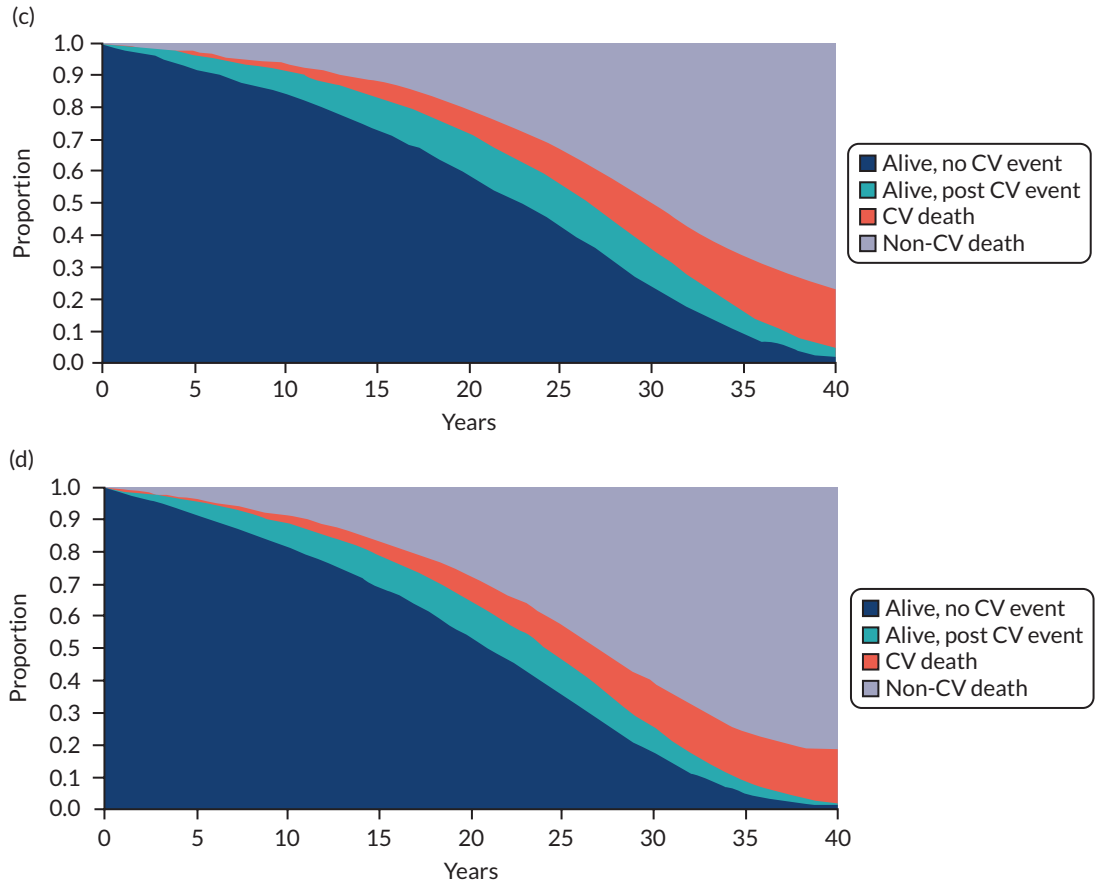

FIGURE 47 State occupancy (no treatment) with and without adjustment for competing risk of non-cardiovascular mortality in example cohorts. (a) 60-year-old men, 10-year cardiovascular risk=10%: unadjusted for competing risk of non-cardiovascular mortality; (b) 60-year-old women, 10-year cardiovascular risk=10%: unadjusted for competing risk of non-cardiovascular mortality; (c) 60-year-old men, 10-year cardiovascular risk=10%: adjusted for competing risk of non-cardiovascular mortality; and (d) 60-year-old women, 10-year cardiovascular risk=10%: adjusted for competing risk of non-cardiovascular mortality. CV, cardiovascular.

Deterministic incremental cost–utility results

Table 56 replicates Table 97 in appendix L of CG181,[10] showing estimated costs and QALYs for each statin strategy and no treatment. *Table 56* also gives NHB for each arm (valuing QALYs at £20,000 each).

In *Figures 48* and *49*, we depict the cost-effectiveness of statins for people of different ages and cardiovascular risks, and how adjusting for competing risk of non-cardiovascular death affects these

TABLE 56 Updated model, including adjustment for competing risk of non-cardiovascular death: cost–utility results in men and women at various levels of non-cardiovascular risk

	60-year-old men			60-year-old women		
Strategy	**Cost (£)**	**QALY**	**NHB**	**Cost (£)**	**QALY**	**NHB**
10-year cardiovascular risk = 30%						
No statins	8590	9.410	8.981	8328	8.630	8.214
Low-intensity statin (S10)	8811	9.598	9.157	8528	8.807	8.380
Medium-intensity statin (S20)	8176	9.721	9.313	7904	8.925	8.530
High-intensity statin (A20)	8114	9.831	9.425	7818	9.031	8.640
High-intensity statin (A80)	8189	9.831	9.422	7890	9.031	8.636

TABLE 56 Updated model, including adjustment for competing risk of non-cardiovascular death: cost–utility results in men and women at various levels of non-cardiovascular risk (*continued*)

	60-year-old men			60-year-old women		
Strategy	**Cost (£)**	**QALY**	**NHB**	**Cost (£)**	**QALY**	**NHB**
10-year cardiovascular risk = 25%						
No statins	8272	10.099	9.685	7935	9.229	8.832
Low-intensity statin (S10)	8604	10.283	9.852	8246	9.400	8.988
Medium-intensity statin (S20)	7985	10.405	10.006	7642	9.517	9.134
High-intensity statin (A20)	7934	10.509	10.112	7565	9.616	9.238
High-intensity statin (A80)	8015	10.509	10.108	7644	9.616	9.234
10-year cardiovascular risk = 20%						
No statins	7914	10.946	10.550	7451	9.946	9.573
Low-intensity statin (S10)	8388	11.125	10.705	7906	10.110	9.715
Medium-intensity statin (S20)	7791	11.245	10.856	7332	10.222	9.856
High-intensity statin (A20)	7755	11.342	10.954	7268	10.313	9.950
High-intensity statin (A80)	7845	11.342	10.950	7354	10.313	9.946
10-year cardiovascular risk = 15%						
No statins	7495	12.025	11.650	6839	10.846	10.504
Low-intensity statin (S10)	8158	12.195	11.787	7486	10.998	10.623
Medium-intensity statin (S20)	7589	12.311	11.932	6954	11.103	10.755
High-intensity statin (A20)	7576	12.398	12.020	6908	11.183	10.837
High-intensity statin (A80)	7676	12.398	12.015	7004	11.183	10.833
10-year cardiovascular risk = 10%						
No statins	6943	13.460	13.113	6013	12.057	11.757
Low-intensity statin (S10)	7868	13.616	13.222	6933	12.191	11.844
Medium-intensity statin (S20)	7336	13.724	13.357	6463	12.284	11.961
High-intensity statin (A20)	7353	13.797	13.429	6443	12.350	12.028
High-intensity statin (A80)	7468	13.797	13.423	6552	12.350	12.022
10-year cardiovascular risk = 9%						
No statins	6794	13.805	13.466	5806	12.360	12.069
Low-intensity statin (S10)	7784	13.957	13.568	6796	12.488	12.149
Medium-intensity statin (S20)	7261	14.062	13.699	6341	12.578	12.261
High-intensity statin (A20)	7286	14.132	13.768	6327	12.640	12.324
High-intensity statin (A80)	7404	14.132	13.762	6439	12.640	12.318
10-year cardiovascular risk = 8%						
No statins	6620	14.174	13.843	5576	12.690	12.411
Low-intensity statin (S10)	7681	14.321	13.937	6643	12.813	12.481
Medium-intensity statin (S20)	7168	14.423	14.065	6206	12.900	12.590
High-intensity statin (A20)	7199	14.489	14.129	6199	12.958	12.648
High-intensity statin (A80)	7322	14.489	14.123	6314	12.958	12.642

continued

TABLE 56 Updated model, including adjustment for competing risk of non-cardiovascular death: cost–utility results in men and women at various levels of non-cardiovascular risk (*continued*)

Strategy	60-year-old men			60-year-old women		
	Cost (£)	QALY	NHB	Cost (£)	QALY	NHB
10-year cardiovascular risk = 7%						
No statins	6409	14.567	14.246	5316	13.055	12.789
Low-intensity statin (S10)	7549	14.708	14.330	6470	13.172	12.848
Medium-intensity statin (S20)	7046	14.806	14.454	6052	13.254	12.952
High-intensity statin (A20)	7085	14.867	14.513	6052	13.308	13.005
High-intensity statin (A80)	7212	14.867	14.507	6172	13.308	12.999
10-year cardiovascular risk = 6%						
No statins	6147	14.983	14.676	5017	13.460	13.209
Low-intensity statin (S10)	7374	15.117	14.748	6268	13.570	13.257
Medium-intensity statin (S20)	6885	15.211	14.867	5872	13.648	13.354
High-intensity statin (A20)	6932	15.267	14.920	5880	13.696	13.402
High-intensity statin (A80)	7063	15.267	14.914	6004	13.696	13.396
10-year cardiovascular risk = 5%						
No statins	5814	15.421	15.131	4662	13.915	13.682
Low-intensity statin (S10)	7139	15.546	15.189	6025	14.017	13.716
Medium-intensity statin (S20)	6668	15.634	15.301	5655	14.089	13.806
High-intensity statin (A20)	6722	15.684	15.348	5671	14.132	13.849
High-intensity statin (A80)	6858	15.684	15.341	5800	14.132	13.842

A20, atorvastatin (20 mg/day); A80, atorvastatin (80 mg/day); S20, simvastatin (20 mg/day).

results. Even before adopting this adjustment, the model suggests that statins represent a good use of resources for almost everyone. It is only for people aged > 60 years with the lowest cardiovascular risk that statins represent poor value for money. However, adjusting for competing risk of non-cardiovascular death removes even this small subgroup. In practice, the distinction is moot if QRISK3 is used to predict cardiovascular risk, as it is essentially impossible for people in those age brackets to have 10-year risks low enough to enter the cost-ineffective zone. If such people did exist, then they would have extraordinary life expectancy, which is why the adjusted model concludes that it would still be good value to offer them statins, as there is every chance that even the oldest people would live to realise their benefit.

With direct treatment disutility

We see the effect of differing DTD assumptions on the cost-effectiveness of statins across a range of ages and baseline cardiovascular event risks in *Figure 50*.

Deterministic sensitivity analysis

One-way sensitivity analysis

One-way sensitivity analyses are depicted in *Figures 51–53*.

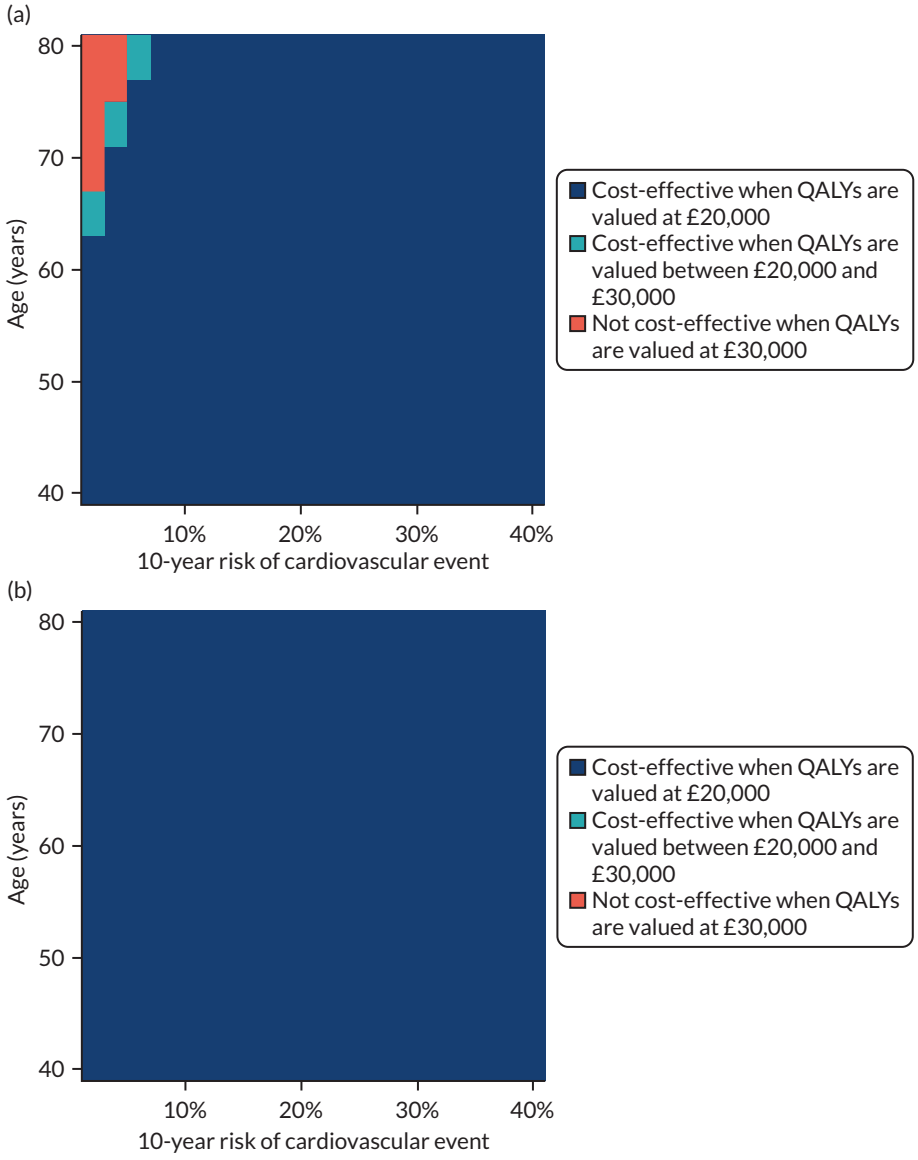

FIGURE 48 Cost-effectiveness of high-intensity statins (atorvastatin 20 mg/day) compared with no treatment, as a function of age and cardiovascular risk. (a) Unadjusted (as per CG181); and (b) adjusted for competing risk of non-cardiovascular death.

Probabilistic sensitivity analysis

Figures 54–57 illustrate the pairwise comparison between high-intensity statins (atorvastatin 20 mg/day) and no treatment with and without adjustment for competing risk of non-cardiovascular death when analysed probabilistically.

With direct treatment disutility

In *Figure 58*, we show probabilistic versions of the pairwise comparison between high-intensity statins (atorvastatin 20 mg/day) and no treatment under varying DTD scenarios for a representative range of age risk profiles.

Scenario analysis

Pay-off time under varying direct treatment disutility assumptions

Figures 59 and *60* show cumulative incremental QALYs over time for four example profiles across our four DTD scenarios.

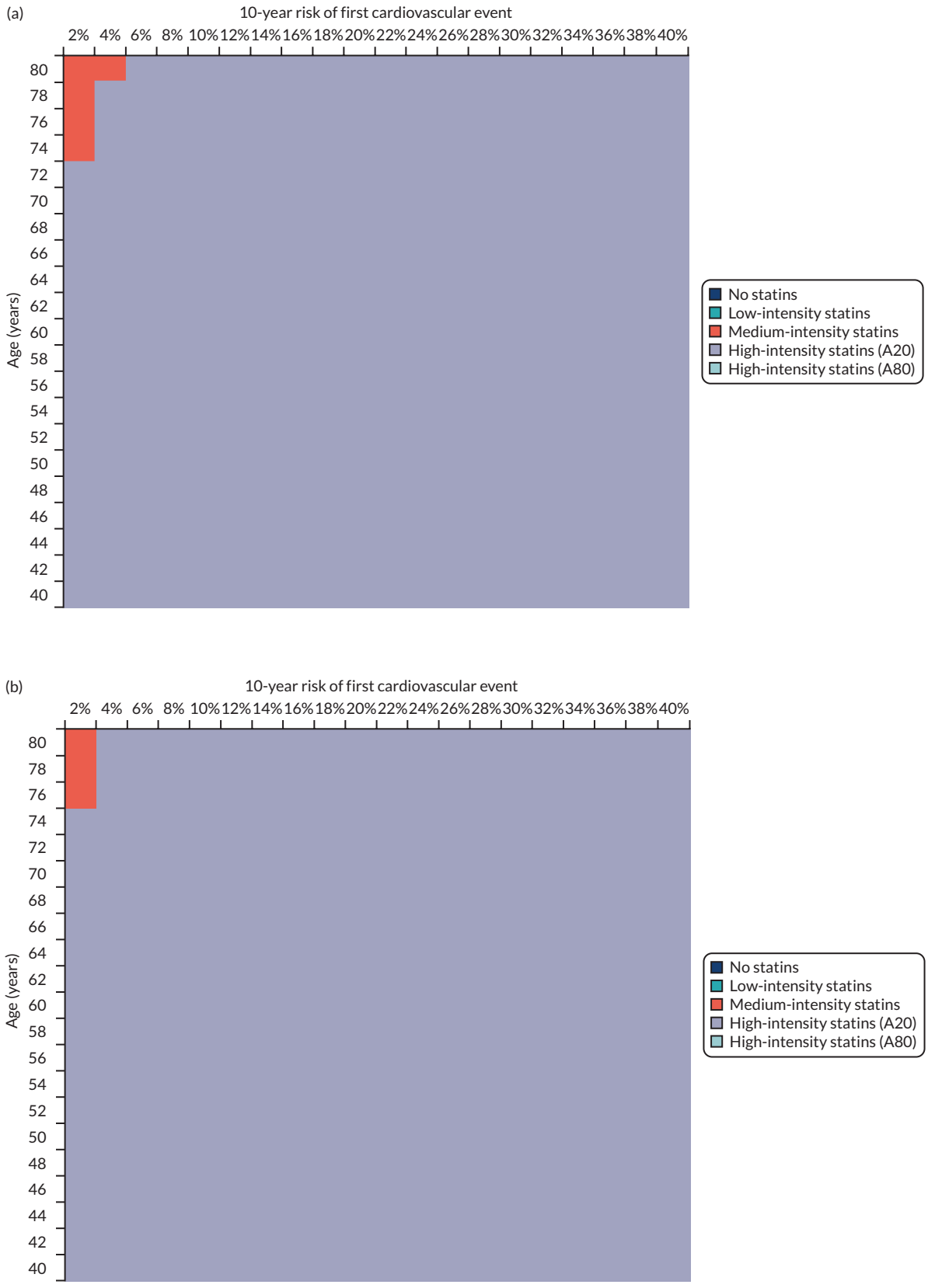

FIGURE 49 Updated CG181 model (not accounting for competing risk or DTD): relationship between age and risk of non-cardiovascular death: cost-effectiveness of statins. (a) Men; and (b) women. Coloured area identifies option with highest net benefit when we value QALYs at £20,000 each.

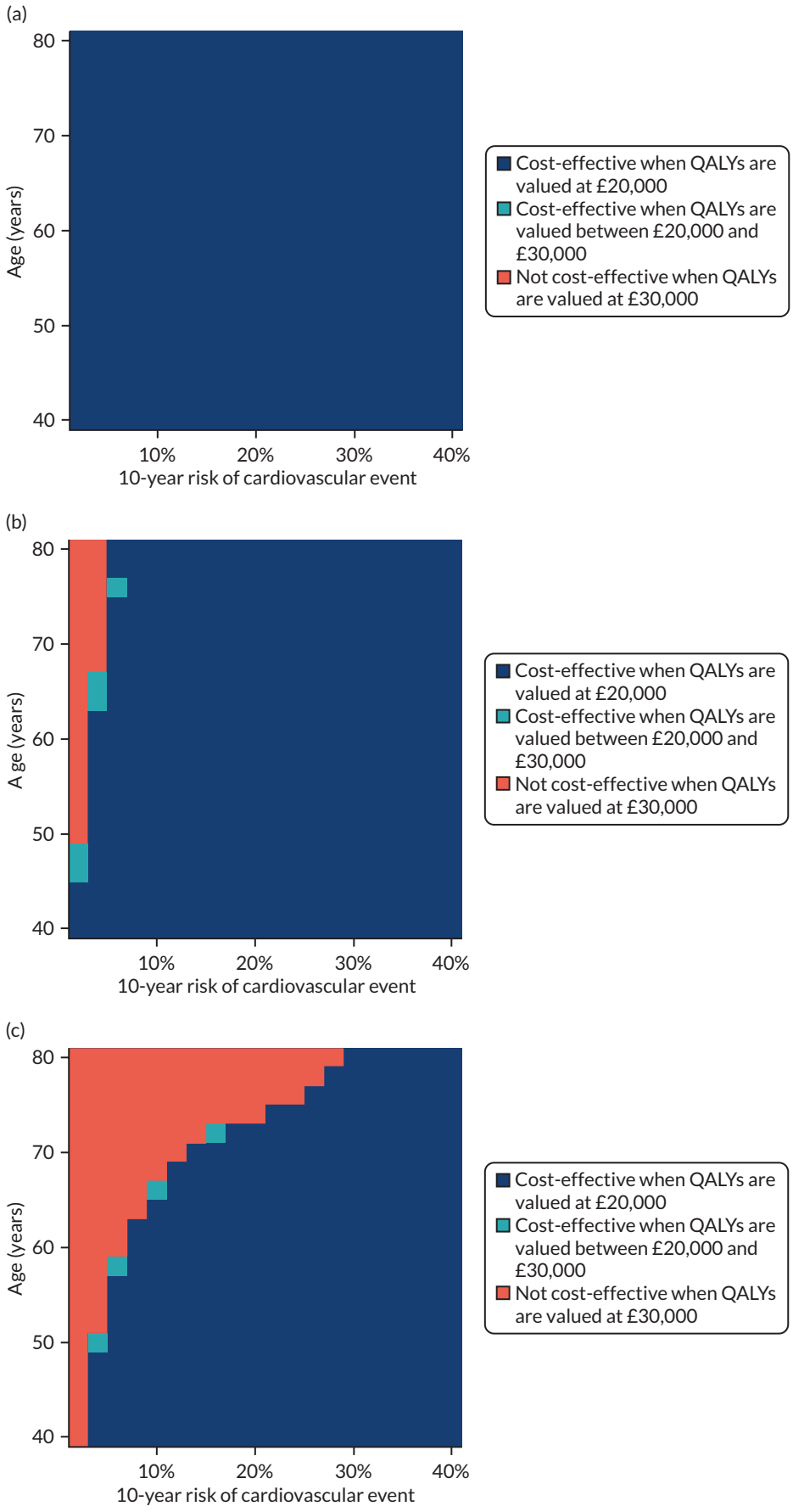

FIGURE 50 Cost-effectiveness of high-intensity statins (atorvastatin 20 mg/day) compared with no treatment, as a function of age, cardiovascular risk and DTD. (a) No DTD; (b) diminishing DTD; (c) time-limited DTD; and (d) permanent DTD. 50 : 50 men : women. All analyses include general model updates and adjustment for non-cardiovascular competing risk. (*continued*)

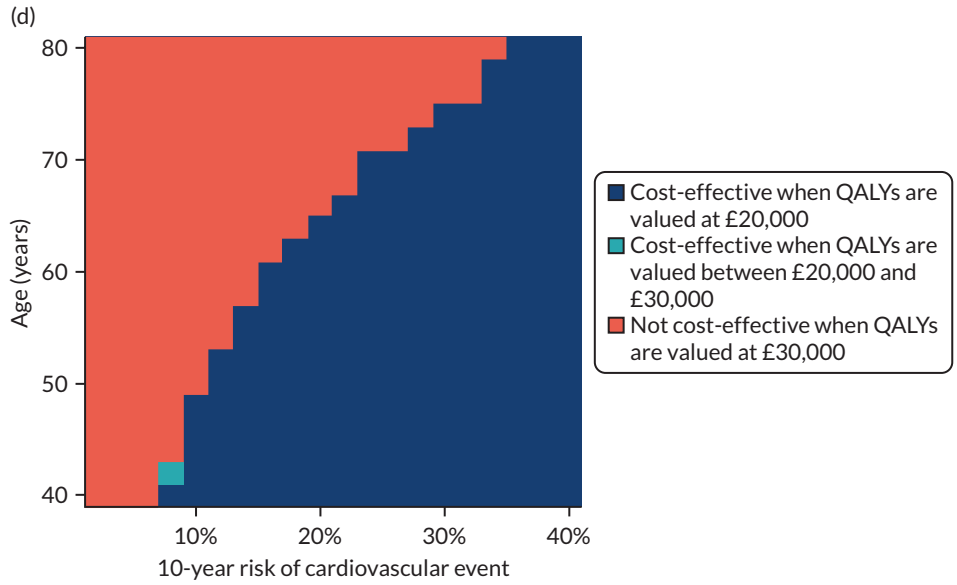

FIGURE 50 Cost-effectiveness of high-intensity statins (atorvastatin 20 mg/day) compared with no treatment, as a function of age, cardiovascular risk and DTD. (a) No DTD; (b) diminishing DTD; (c) time-limited DTD; and (d) permanent DTD. 50 : 50 men : women. All analyses include general model updates and adjustment for non-cardiovascular competing risk.

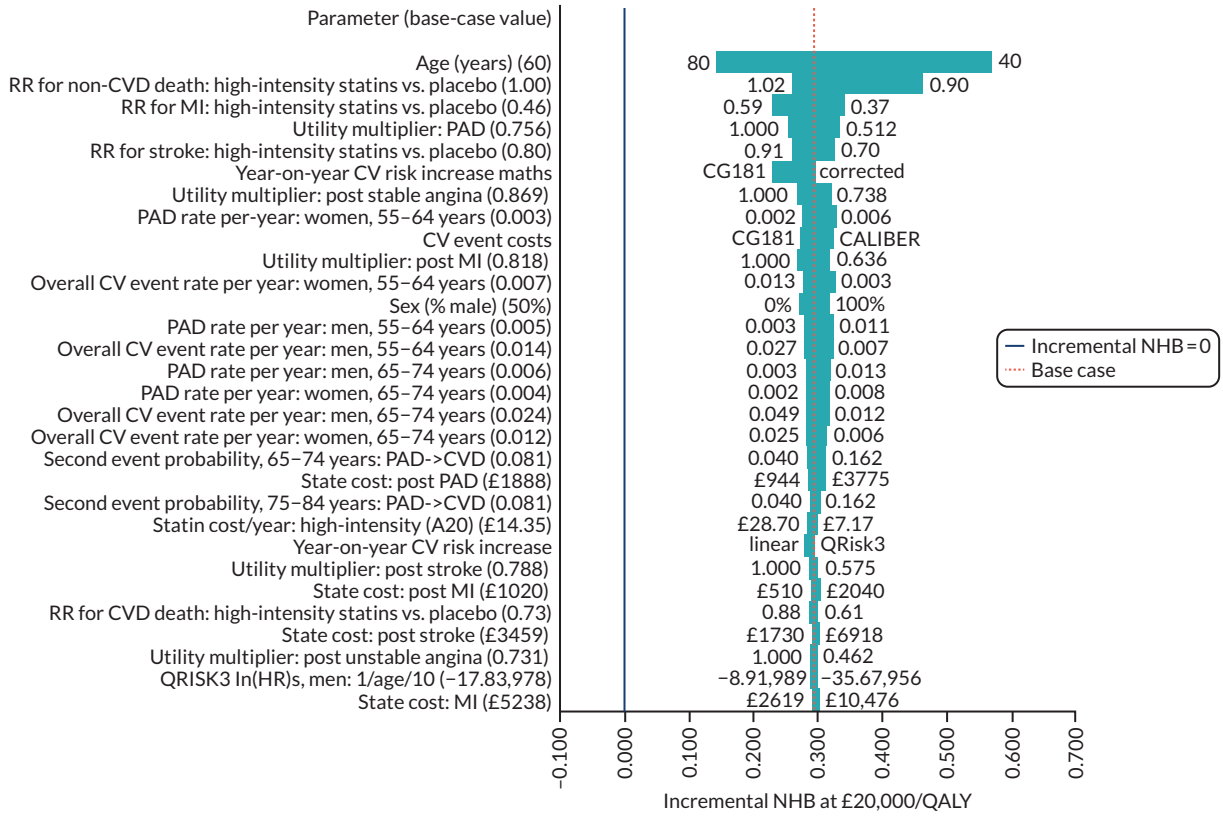

FIGURE 51 Updated model, including adjustment for competing risk of non-cardiovascular death: one-way sensitivity analysis for high-intensity statins (atorvastatin 20 mg/day) compared with no treatment (60-year-olds, 50 : 50 men : women, 10% 10-year cardiovascular event risk). Thirty most influential parameters shown. Positive incremental NHB implies that high-intensity statins is the preferred option (i.e. it would be associated with an ICER of £20,000/QALY or better vs. no treatment). CV, cardiovascular; RR, relative risk.

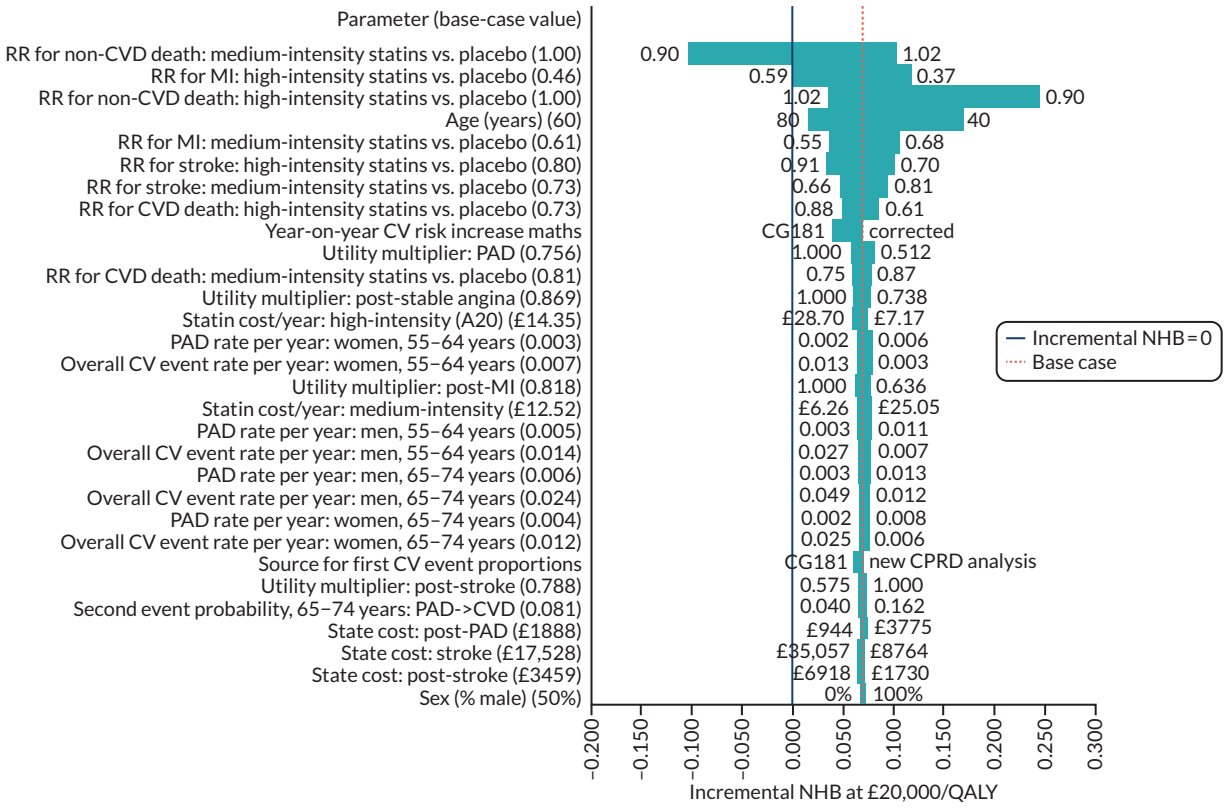

FIGURE 52 Updated model, including adjustment for competing risk of non-cardiovascular death: one-way sensitivity analysis for high-intensity statins (atorvastatin 20 mg/day) compared with medium-intensity statins (simvastatin 20 mg/day) (60-year-olds, 50 : 50 men : women, 10% 10-year cardiovascular event risk). Thirty most influential parameters shown. Positive incremental NHB implies that high-intensity statins is the preferred option (i.e. it would be associated with an ICER of £20,000/QALY or better vs. no treatment). CV, cardiovascular; RR, relative risk.

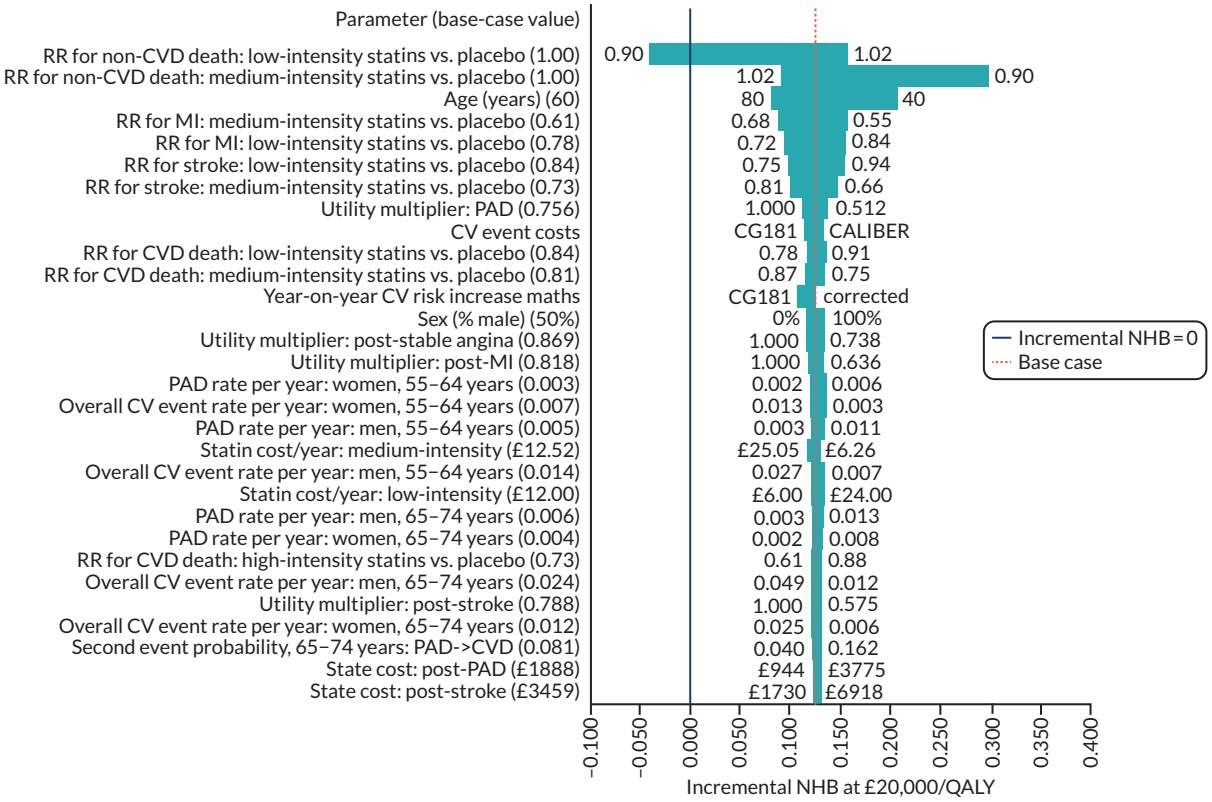

FIGURE 53 Updated model, including adjustment for competing risk of non-cardiovascular death: one-way sensitivity analysis for medium-intensity statins (simvastatin 20 mg/day) compared with low-intensity statins (simvastatin 10 mg/day) (60-year-olds, 50 : 50 men : women, 10% 10-year cardiovascular event risk). Thirty most influential parameters shown. Positive incremental NHB implies that high-intensity statins is the preferred option (i.e. it would be associated with an ICER of £20,000/QALY or better vs. no treatment). CV, cardiovascular; RR, relative risk.

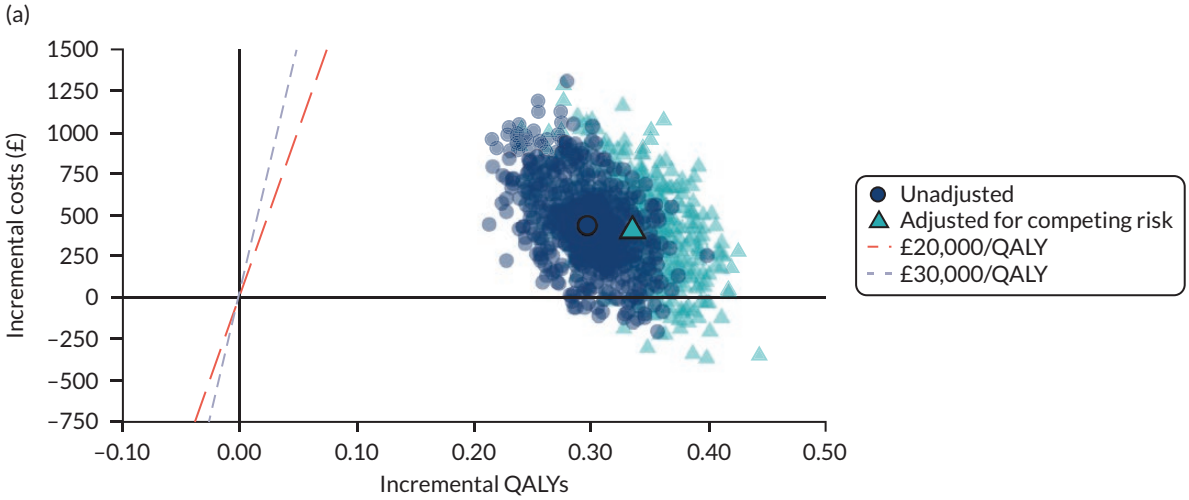

FIGURE 54 Probabilistic sensitivity analysis for high-intensity statins (atorvastatin 20 mg/day vs. no treatment) with and without adjustment for competing risk of non-cardiovascular death in example cohorts. (a) cost–utility scatterplot for 60-year-old men, 10-year cardiovascular risk = 10%; (b) cost–utility scatterplot for 60-year-old women, 10-year cardiovascular risk = 10%; (c) cost-effectiveness acceptability curves for 60-year-old men, 10-year cardiovascular risk = 10%; and (d) cost-effectiveness acceptability curves for 60-year-old women, 10-year cardiovascular risk = 10%.

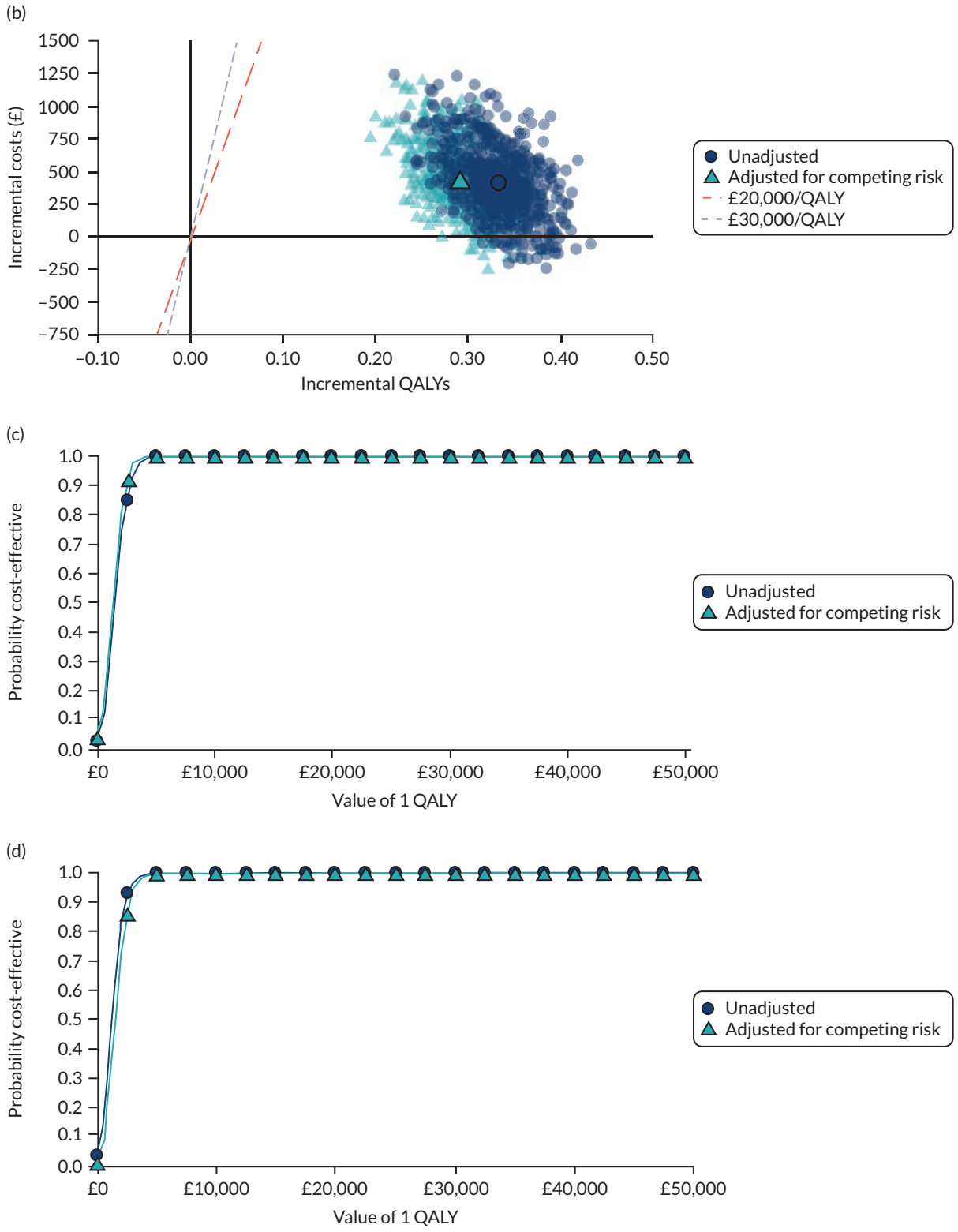

FIGURE 54 Probabilistic sensitivity analysis for high-intensity statins (atorvastatin 20 mg/day vs. no treatment) with and without adjustment for competing risk of non-cardiovascular death in example cohorts. (a) cost–utility scatterplot for 60-year-old men, 10-year cardiovascular risk = 10%; (b) cost–utility scatterplot for 60-year-old women, 10-year cardiovascular risk = 10%; (c) cost-effectiveness acceptability curves for 60-year-old men, 10-year cardiovascular risk = 10%; and (d) cost-effectiveness acceptability curves for 60-year-old women, 10-year cardiovascular risk = 10%.

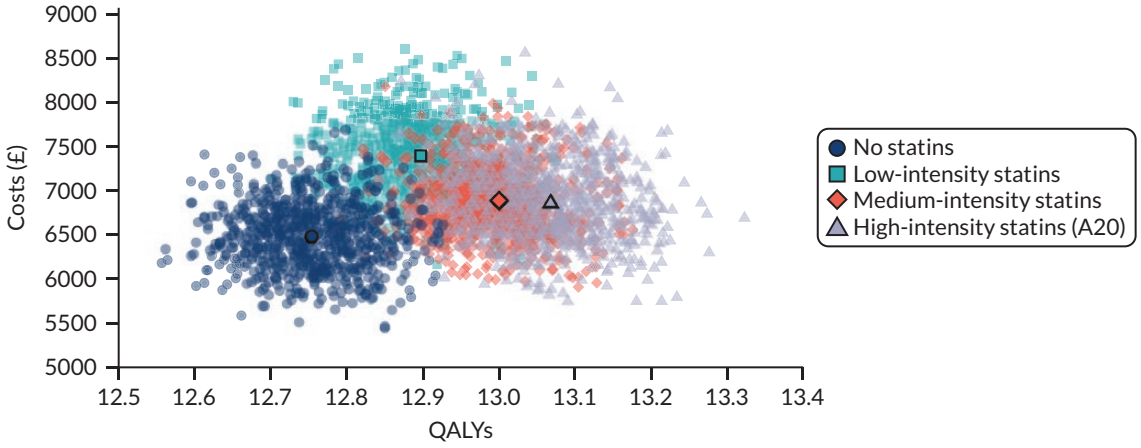

FIGURE 55 Updated model, including adjustment for competing risk of non-cardiovascular death: probabilistic cost–utility scatterplot for all options (60-year-olds, 50 : 50 men : women, 10% 10-year cardiovascular event risk).

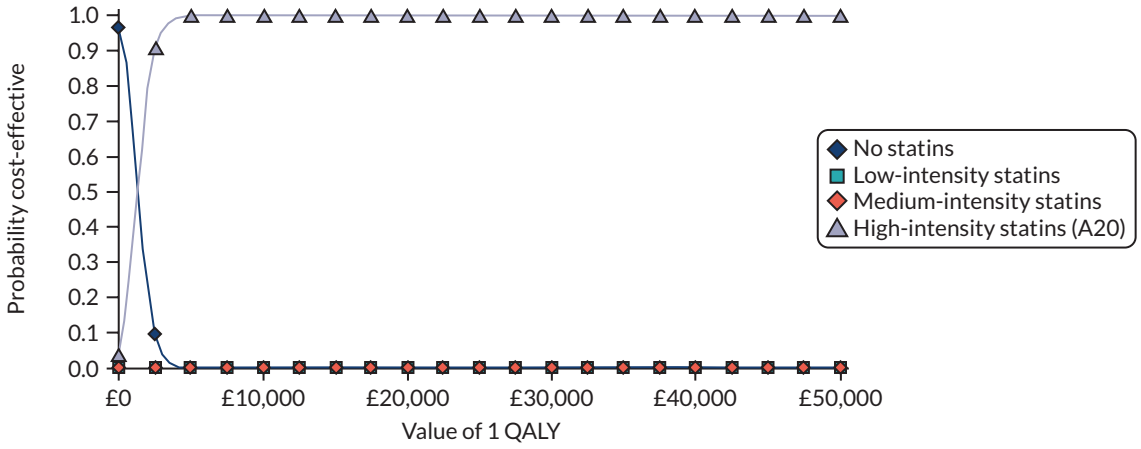

FIGURE 56 Updated model, including adjustment for competing risk of non-cardiovascular death: cost-effectiveness acceptability curve (60-year-olds, 50 : 50 men : women, 10% 10-year cardiovascular event risk). Bold line shows cost-effectiveness acceptability frontier.

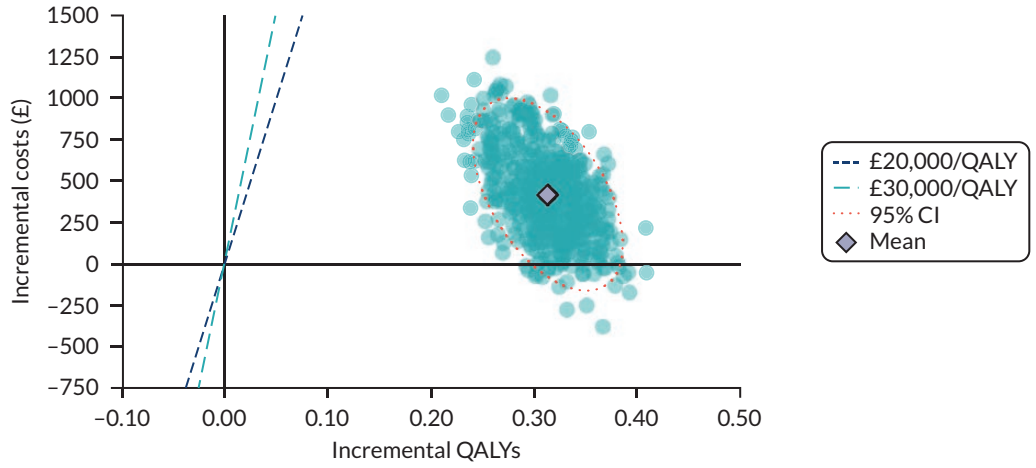

FIGURE 57 Updated model, including adjustment for competing risk of non-cardiovascular death: probabilistic incremental cost–utility scatterplot – high-intensity statins (atorvastatin 20 mg/day) compared with no treatment (60-year-olds, 50 : 50 men : women, 10% 10-year cardiovascular event risk).

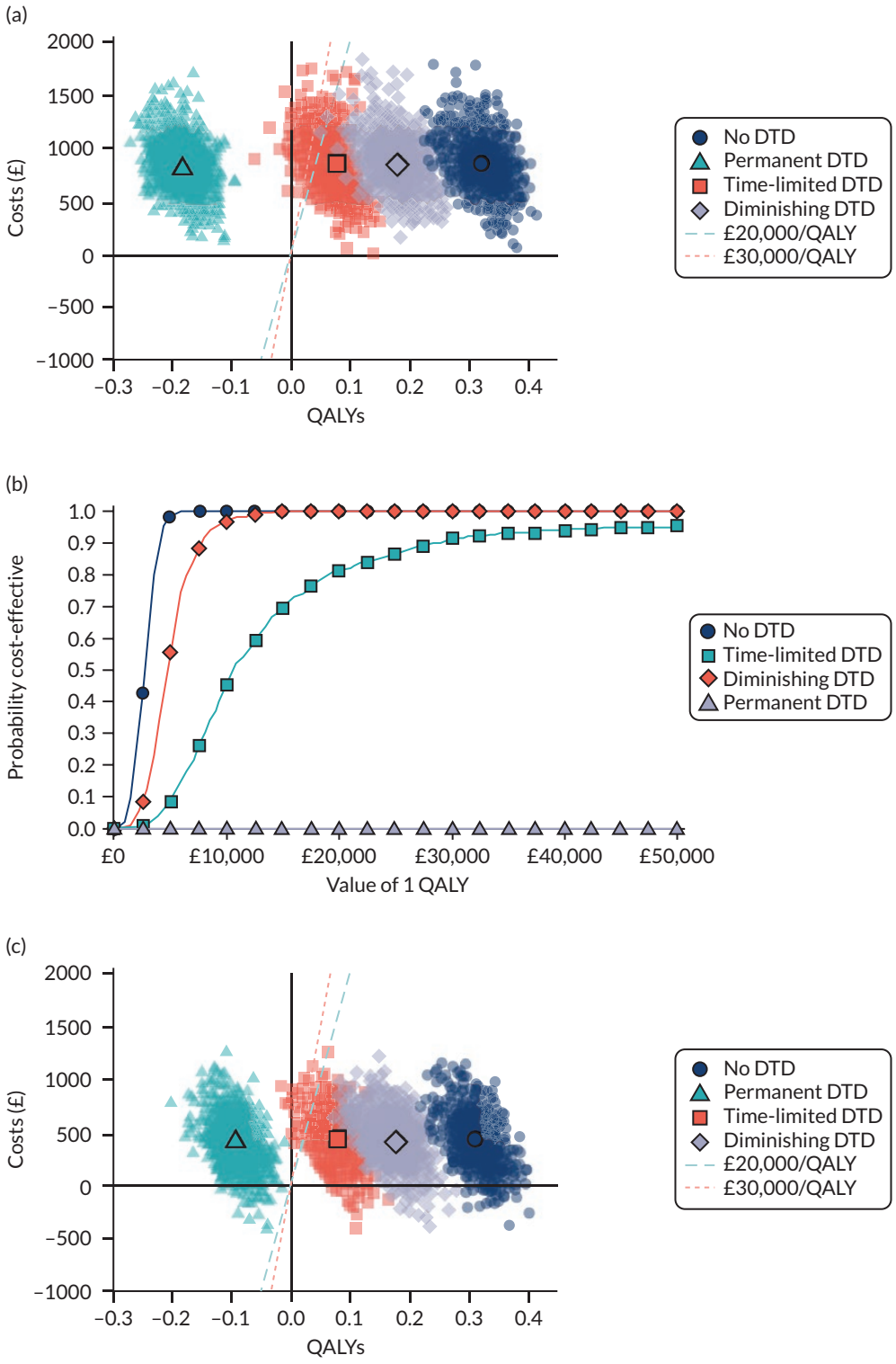

FIGURE 58 Probabilistic sensitivity analysis for high-intensity statins (atorvastatin 20 mg/day vs. no treatment) under varying DTD scenarios for example cohorts. (a) Cost–utility scatterplot for 50-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 5%; (b) cost-effectiveness acceptability curves for 50-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 5%; (c) cost–utility scatterplot for 60-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 10%; and (d) cost-effectiveness acceptability curves for 60-year-olds, 50 : 50 men women, 10-year cardiovascular risk = 10%; (e) cost–utility scatterplot for 70-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 20%; (f) cost-effectiveness acceptability curves for 70-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 20%; (g) cost–utility scatterplot for 80-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 30%; and (h) cost-effectiveness acceptability curves for 80-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 30%. (*continued*)

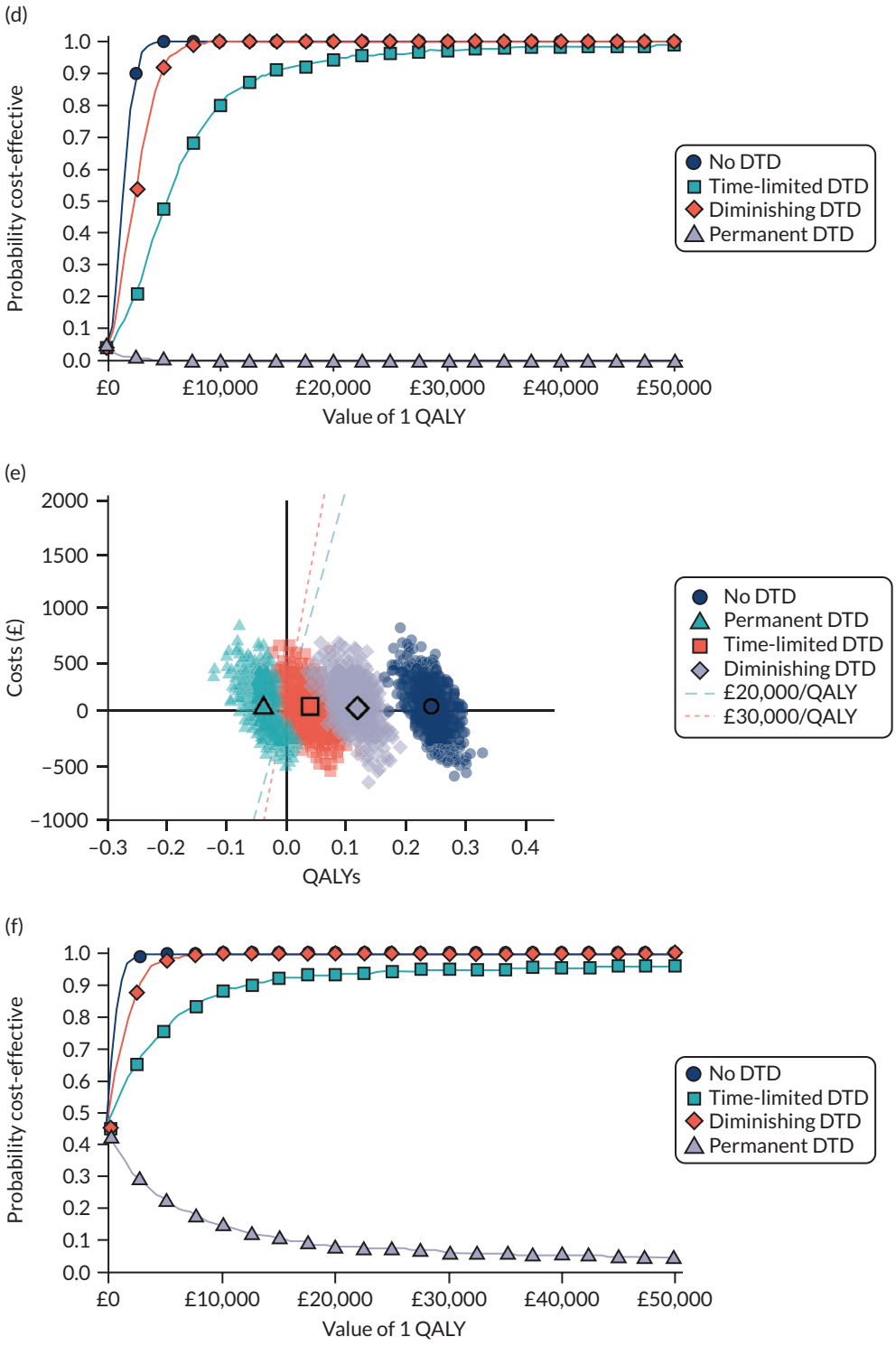

FIGURE 58 Probabilistic sensitivity analysis for high-intensity statins (atorvastatin 20 mg/day vs. no treatment) under varying DTD scenarios for example cohorts. (a) Cost–utility scatterplot for 50-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 5%; (b) cost-effectiveness acceptability curves for 50-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 5%; (c) cost–utility scatterplot for 60-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 10%; and (d) cost-effectiveness acceptability curves for 60-year-olds, 50 : 50 men women, 10-year cardiovascular risk = 10%; (e) cost–utility scatterplot for 70-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 20%; (f) cost-effectiveness acceptability curves for 70-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 20%; (g) cost–utility scatterplot for 80-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 30%; and (h) cost-effectiveness acceptability curves for 80-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 30%. (*continued*)

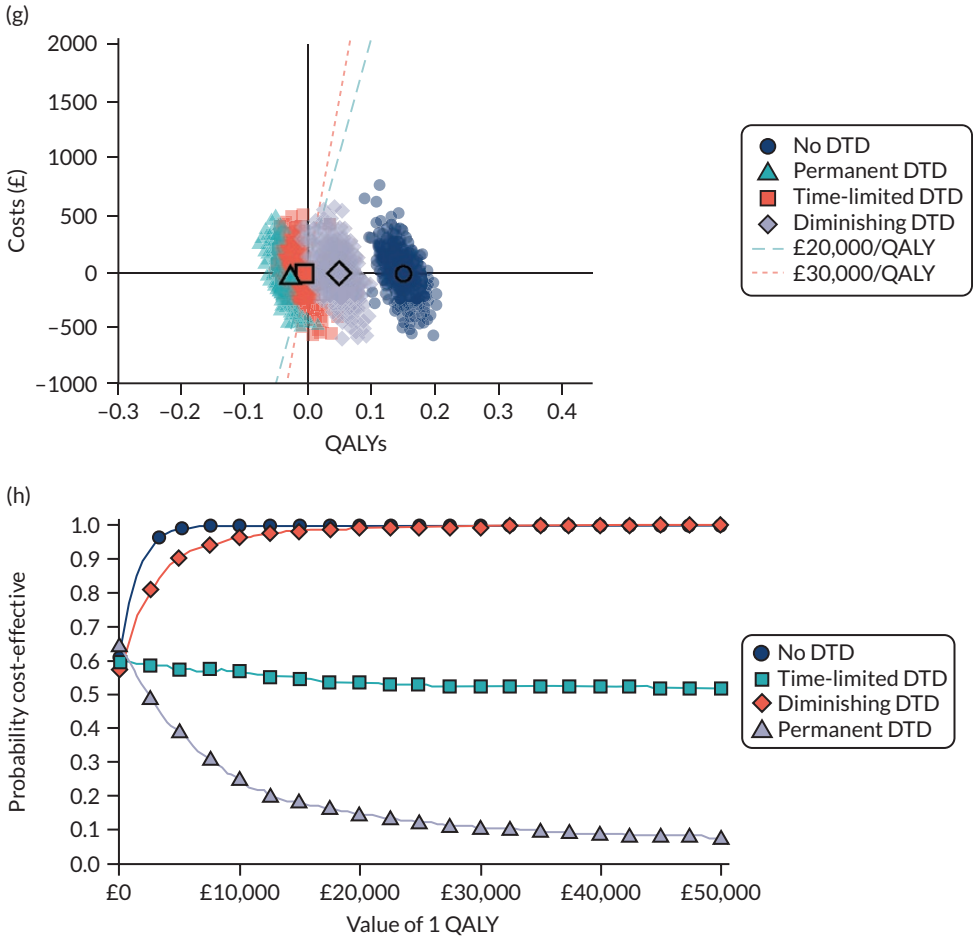

FIGURE 58 Probabilistic sensitivity analysis for high-intensity statins (atorvastatin 20 mg/day vs. no treatment) under varying DTD scenarios for example cohorts. (a) Cost–utility scatterplot for 50-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 5%; (b) cost-effectiveness acceptability curves for 50-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 5%; (c) cost–utility scatterplot for 60-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 10%; and (d) cost-effectiveness acceptability curves for 60-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 10%; (e) cost–utility scatterplot for 70-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 20%; (f) cost-effectiveness acceptability curves for 70-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 20%; (g) cost–utility scatterplot for 80-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 30%; and (h) cost-effectiveness acceptability curves for 80-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 30%.

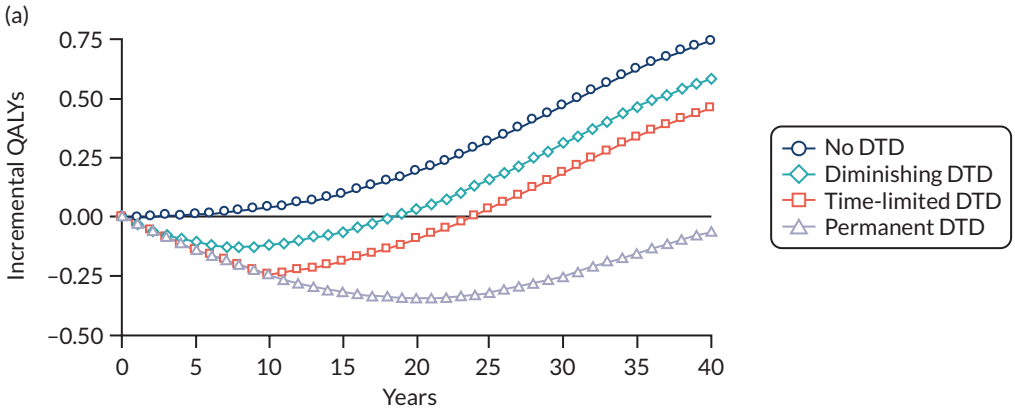

FIGURE 59 Payoff time for high-intensity statins (atorvastatin 20 mg/day) compared with no treatment, for different example populations under different DTD scenarios. (a) Undiscounted cumulative incremental QALYs for 50-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 5%; (b) undiscounted cumulative incremental NHB for 50-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 5%; (c) undiscounted cumulative incremental QALYs for 60-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 10%; and (d) undiscounted cumulative incremental NHB for 60-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 10%; (e) undiscounted cumulative incremental QALYs for 70-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 20%; (f) undiscounted cumulative incremental NHB for 70-year-olds, 50 : 50 men : women, 10-year cardiovascular risk= 20%; (g) undiscounted cumulative incremental QALYs for 80-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 30%; and (h) undiscounted cumulative incremental NHB for 80-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 30%. (*continued*)

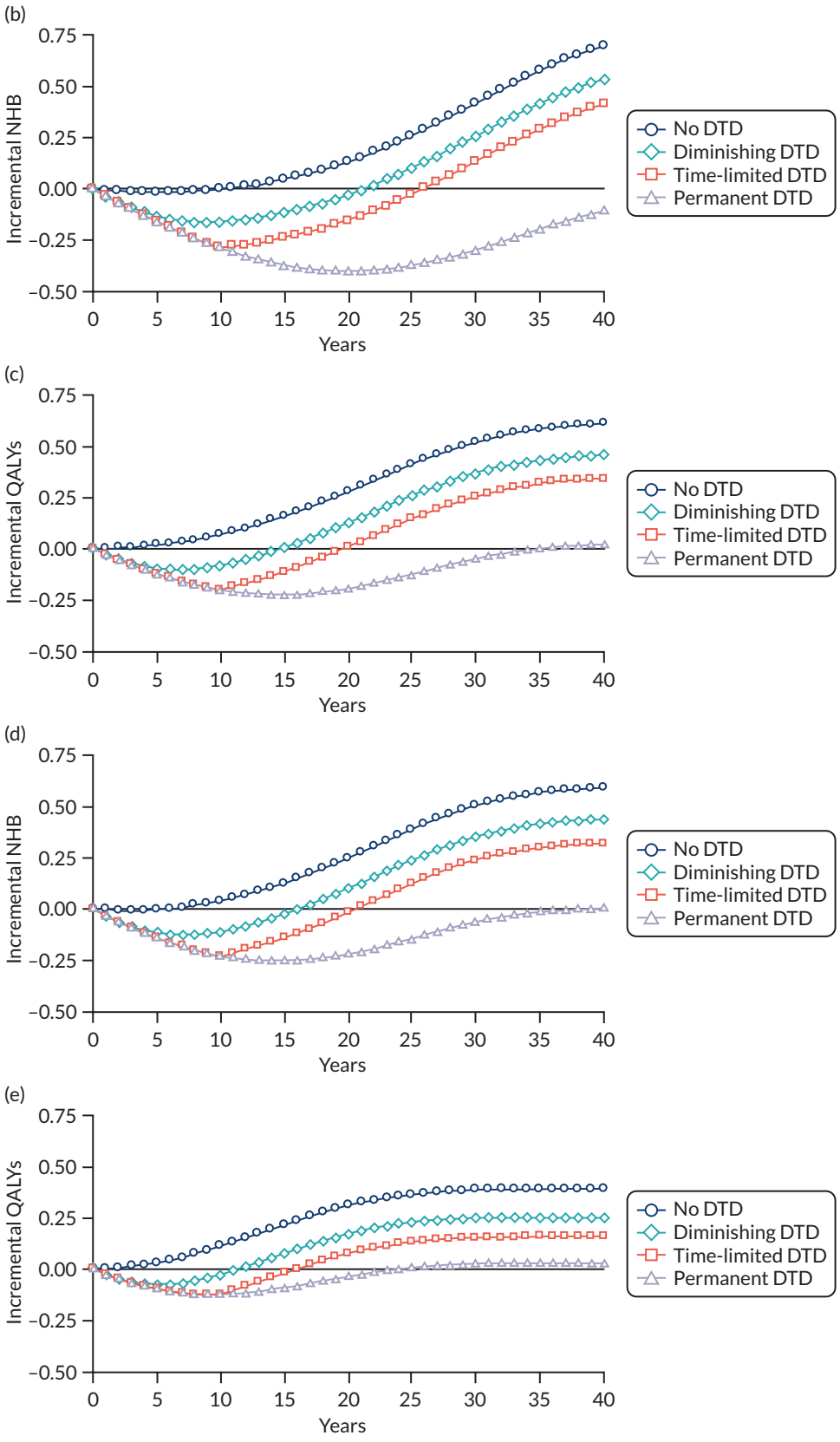

FIGURE 59 Payoff time for high-intensity statins (atorvastatin 20 mg/day) compared with no treatment, for different example populations under different DTD scenarios. (a) Undiscounted cumulative incremental QALYs for 50-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 5%; (b) undiscounted cumulative incremental NHB for 50-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 5%; (c) undiscounted cumulative incremental QALYs for 60-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 10%; and (d) undiscounted cumulative incremental NHB for 60-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 10%; (e) undiscounted cumulative incremental QALYs for 70-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 20%; (f) undiscounted cumulative incremental NHB for 70-year-olds, 50 : 50 men : women, 10-year cardiovascular risk= 20%; (g) undiscounted cumulative incremental QALYs for 80-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 30%; and (h) undiscounted cumulative incremental NHB for 80-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 30%. (*continued*)

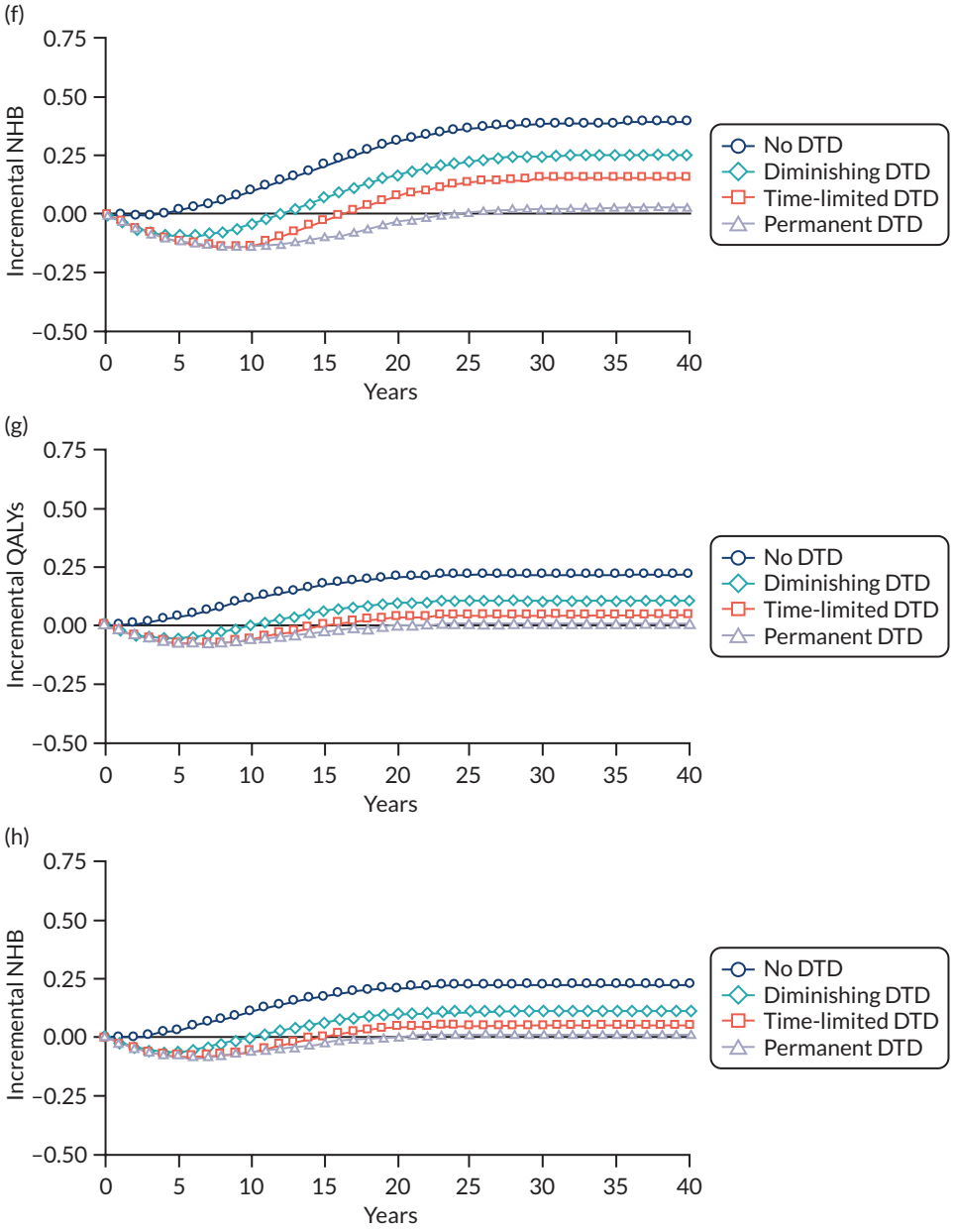

FIGURE 59 Payoff time for high-intensity statins (atorvastatin 20 mg/day) compared with no treatment, for different example populations under different DTD scenarios. (a) Undiscounted cumulative incremental QALYs for 50-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 5%; (b) undiscounted cumulative incremental NHB for 50-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 5%; (c) undiscounted cumulative incremental QALYs for 60-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 10%; and (d) undiscounted cumulative incremental NHB for 60-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 10%; (e) undiscounted cumulative incremental QALYs for 70-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 20%; (f) undiscounted cumulative incremental NHB for 70-year-olds, 50 : 50 men : women, 10-year cardiovascular risk= 20%; (g) undiscounted cumulative incremental QALYs for 80-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 30%; and (h) undiscounted cumulative incremental NHB for 80-year-olds, 50 : 50 men : women, 10-year cardiovascular risk = 30%. (*continued*)

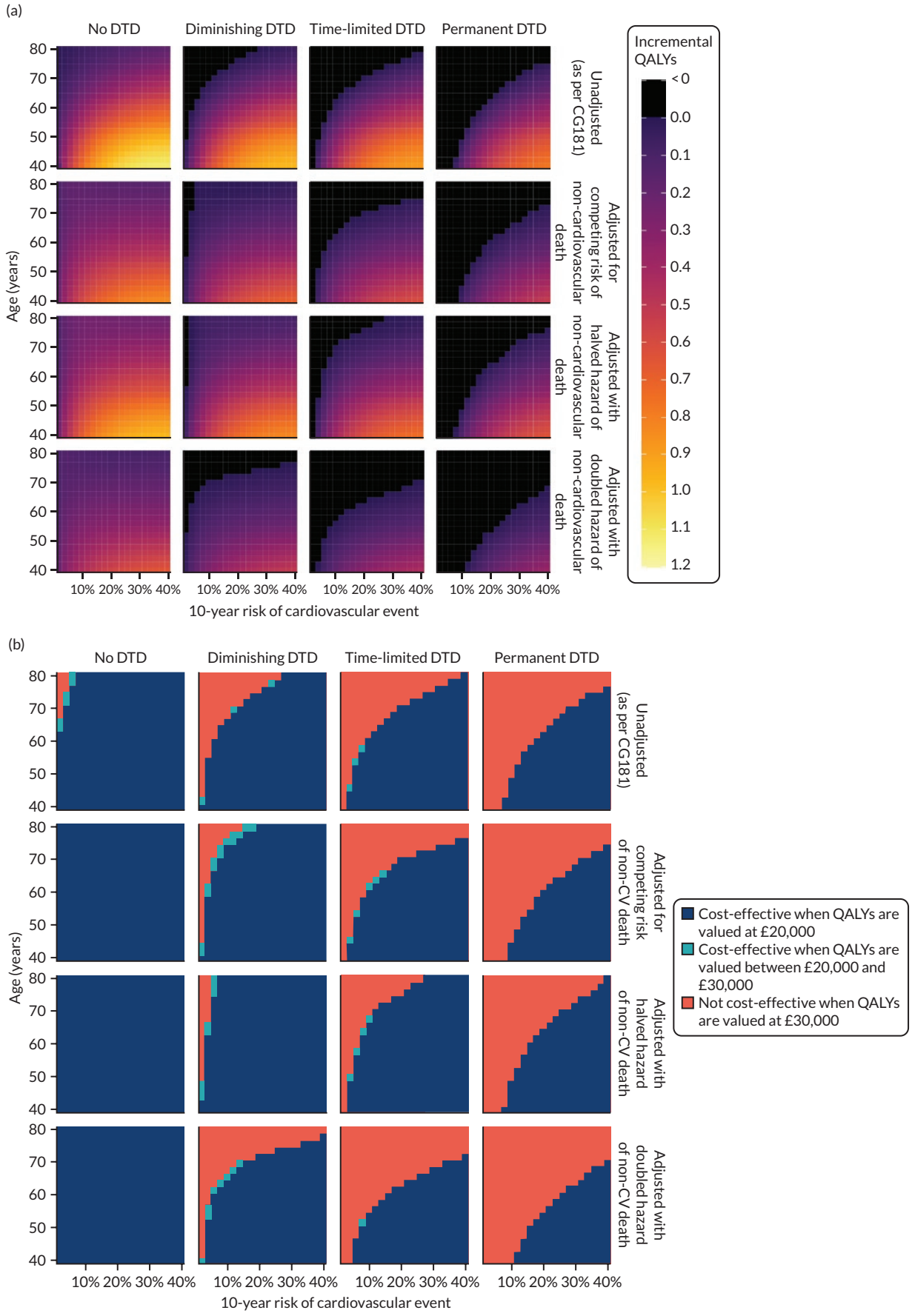

FIGURE 60 Clinical effectiveness and cost-effectiveness of high-intensity statins, as a function of age and cardiovascular risk, with different levels of DTD (as absolute decrement) and competing risk of non-cardiovascular death. (a) Effectiveness (incremental QALYs); and (b) cost-effectiveness (when QALYs are valued at £20,000–30,000).

Appendix 9 Supplementary methods and results for model assessing cost-effectiveness of bisphosphonates for the primary prevention of osteoporotic fragility fracture

Supplementary methods

Accounting for competing risk of non-cardiovascular death

As explained in the main text (see *Accounting for competing risk of non-cardiovascular death*, p.91), the critical covariate for our relative survival models is Δlogit(Q), that is the difference between an individual's predicted 10-year QFracture-2012 score and the average score for a person of the same age and sex. We estimate the latter using a regression on the CPRD data set. *Table 57* shows the model coefficients and *Figure 61* shows the model fitted for men and women as a function of age.

TABLE 57 Regression estimating population average logit(QFracture-2012 10-year risk of MOF) as a function of sex and age

Parameter	Fitted to all ages, estimate (95% CI)	Fitted to people aged < 90 years only, estimate (95% CI)
Intercept	−2.27 (−4.47 to −0.06)	−5.70 (−5.77 to −5.63)
Age	−0.509 (−0.797 to −0.220)	−0.065 (−0.070 to −0.059)
Age^2	2.82×10^{-2} (1.24×10^{-2} to 4.39×10^{-2})	3.45×10^{-3} (3.30×10^{-3} to 3.60×10^{-3})
Age^3	-8.09×10^{-4} (-1.27×10^{-3} to -3.44×10^{-4})	-3.75×10^{-5} (-3.92×10^{-5} to -3.57×10^{-5})
Age^4	1.48×10^{-5} (6.74×10^{-6} to 2.28×10^{-5})	1.53×10^{-7} (1.45×10^{-7} to 1.61×10^{-7})
Age^5	-1.68×10^{-7} (-2.49×10^{-7} to -8.66×10^{-8})	
Age^6	1.07×10^{-9} (6.27×10^{-10} to 1.52×10^{-9})	
Age^7	-2.93×10^{-12} (-3.97×10^{-12} to -1.90×10^{-12})	
Male	18.48 (15.18 to 21.79)	4.63 (4.53 to 4.73)
Male × age	−2.053 (−2.488 to −1.619)	−0.232 (−0.240 to −0.224)
Male × age^2	1.03×10^{-1} (7.93×10^{-2} to 1.27×10^{-1})	3.57×10^{-3} (3.36×10^{-3} to 3.79×10^{-3})
Male × age^3	-2.97×10^{-3} (-3.68×10^{-3} to -2.26×10^{-3})	-2.91×10^{-5} (-3.17×10^{-5} to -2.65×10^{-5})
Male × age^4	5.06×10^{-5} (3.83×10^{-5} to 6.30×10^{-5})	1.20×10^{-7} (1.08×10^{-7} to 1.31×10^{-7})
Male × age^5	-5.07×10^{-7} (-6.33×10^{-7} to -3.81×10^{-7})	
Male × age^6	2.76×10^{-9} (2.06×10^{-9} to 3.46×10^{-9})	
Male × age^7	-6.27×10^{-12} (-7.90×10^{-12} to -4.64×10^{-12})	

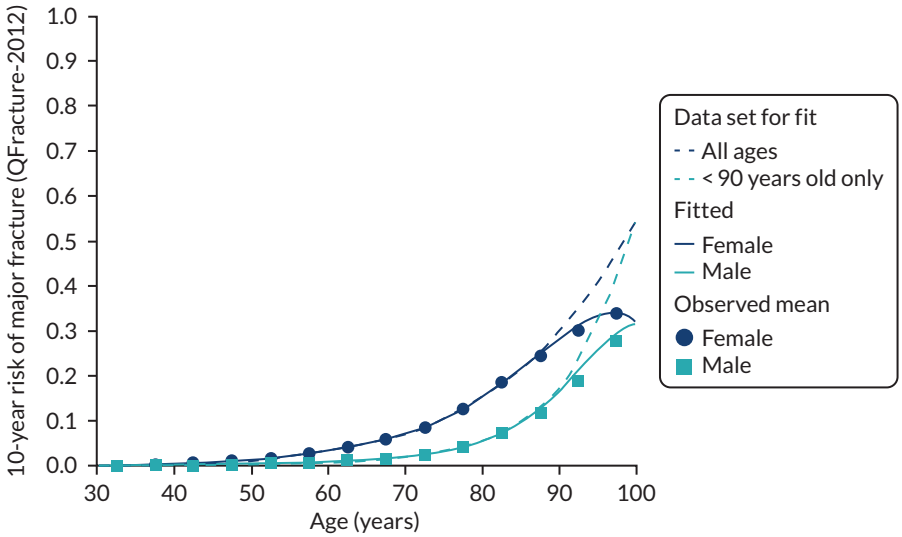

FIGURE 61 Average 10-year risk of MOF (QFracture-2012) as a function of age and sex.

Supplementary results

Threshold at which treatment becomes associated with positive net benefit according to the generalised additive model adjusting for age and fracture risk

The threshold at which treatment becomes associated with positive net benefit according to the GAM and adjusting for age and fracture risk is shown in *Table 58*.

Cost-effectiveness of bisphosphonates for the primary prevention of osteoporotic fragility fracture: meta-model accounting for age, sex and baseline fracture risk

The meta-model takes the form:

$$g\left(E\left[INMB\right]\right) = \beta_0 + f\left(QFrac, Age\right) Adj.Sex. \tag{18}$$

Figure 62 shows the fitted model for men and women at indicative ages of 50, 60, 70 and 80 years, and *Table 59* tabulates the threshold at which net benefit becomes positive (assuming that decision-makers value QALYs at £20,000 each).

TABLE 58 Outputs of the GAM, adjusting for age and fracture risk: threshold at which alendronate becomes cost-effective compared with no treatment

Age (years)	Unadjusted threshold (95% CI)	Adjusted for competing risk of non-fracture death threshold (95% CI)
40	4.9 (4 to 6.7)	8.5 (5.5 to inf[a])
50	5.1 (4.5 to 6.4)	8.5 (6.1 to 17)
60	5.5 (5 to 6.1)	7.4 (6.2 to 9.4)
70	4.6 (4.2 to 4.9)	4.6 (4.2 to 4.9)
80	4.1 (3.4 to 4.6)	4.2 (3.7 to 4.7)
90	8.8 (0 to 12)	8.3 (0 to 12)

inf, infinity.
a The upper limit of CI suggests that there is no level of risk at which the intervention would become cost-effective.

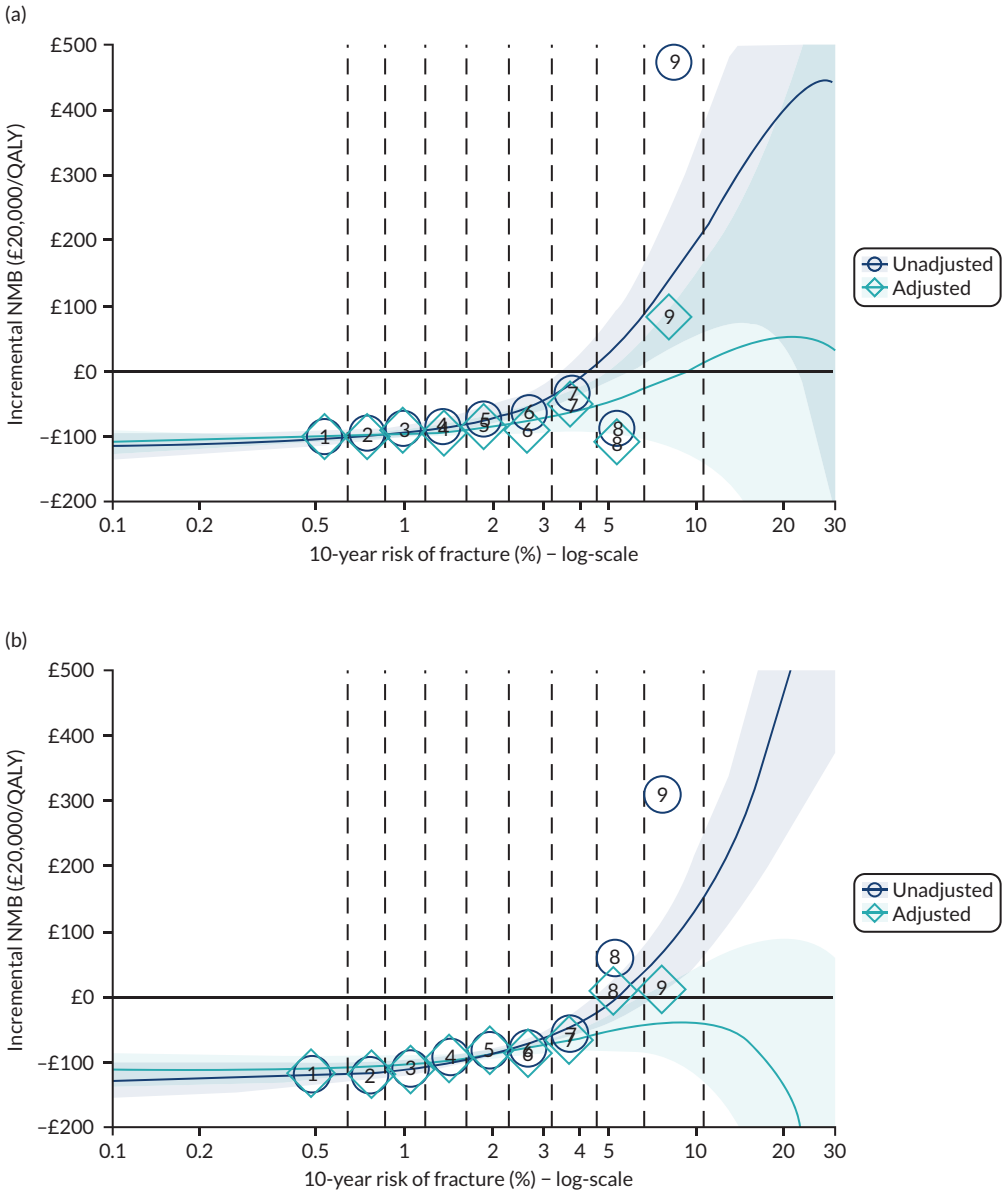

FIGURE 62 Cost-effectiveness of bisphosphonates (incremental net monetary benefit compared with no treatment) as a function of age, sex and risk of fracture, with different assumptions about competing risk of non-fracture death. (a) Men aged 50 years; (b) women aged 50 years; (c) men aged 60 years; (d) women aged 60 years; (e) men aged 70 years; (f) women aged 70 years; (g) men aged 80 years; and (h) women aged 80 years. GAM fitted to model outputs comprising 5 million simulated patients. Lines show fitted model prediction, shaded areas show 95% CI, vertical dashed bars represent deciles of risk and numbered shapes show mean values for people within each tenth of the population (where these are missing, fewer than 100 of the total 5 million simulated people fell into the group). (*continued*)

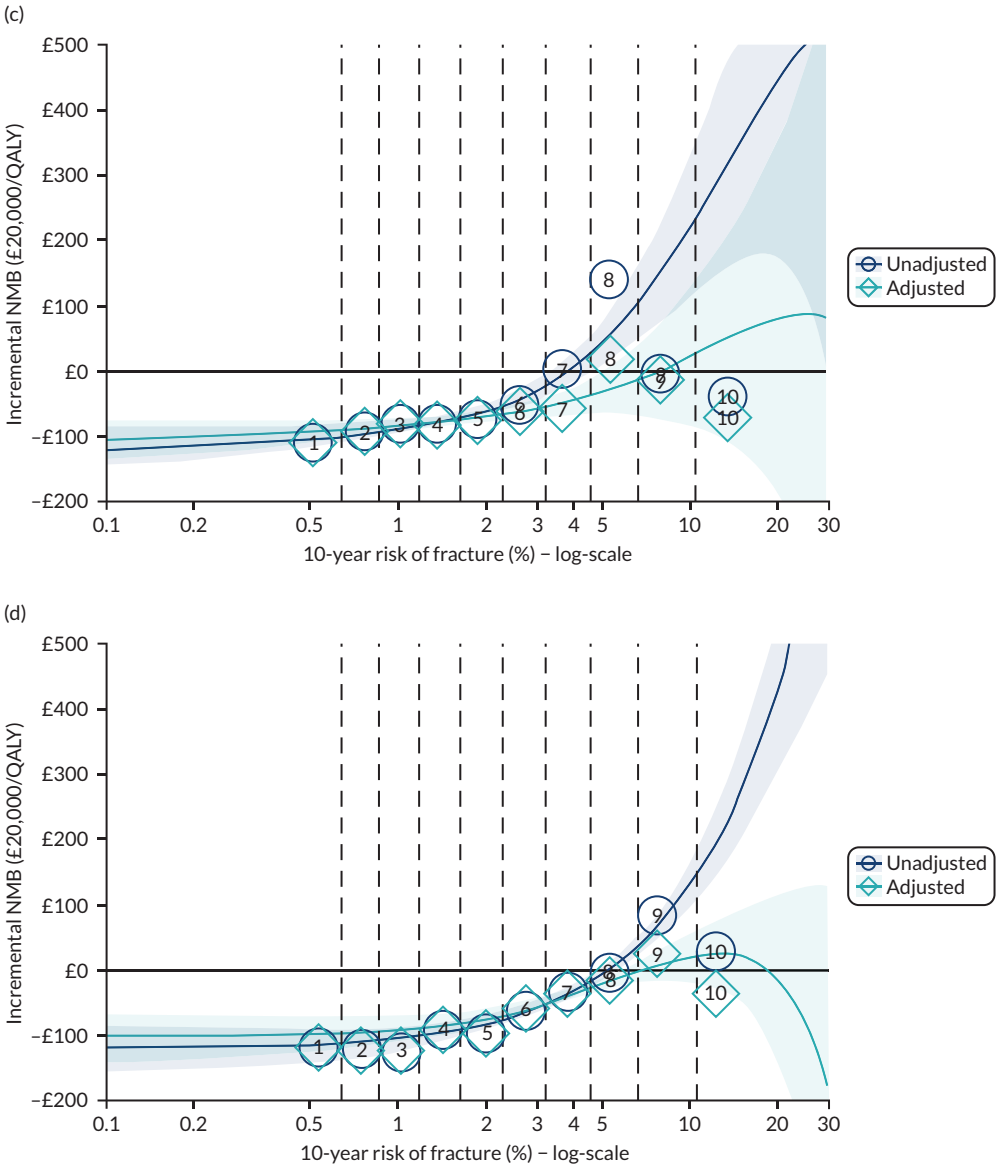

FIGURE 62 Cost-effectiveness of bisphosphonates (incremental net monetary benefit compared with no treatment) as a function of age, sex and risk of fracture, with different assumptions about competing risk of non-fracture death. (a) Men aged 50 years; (b) women aged 50 years; (c) men aged 60 years; (d) women aged 60 years; (e) men aged 70 years; (f) women aged 70 years; (g) men aged 80 years; and (h) women aged 80 years. GAM fitted to model outputs comprising 5 million simulated patients. Lines show fitted model prediction, shaded areas show 95% CI, vertical dashed bars represent deciles of risk and numbered shapes show mean values for people within each tenth of the population (where these are missing, fewer than 100 of the total 5 million simulated people fell into the group). (*continued*)

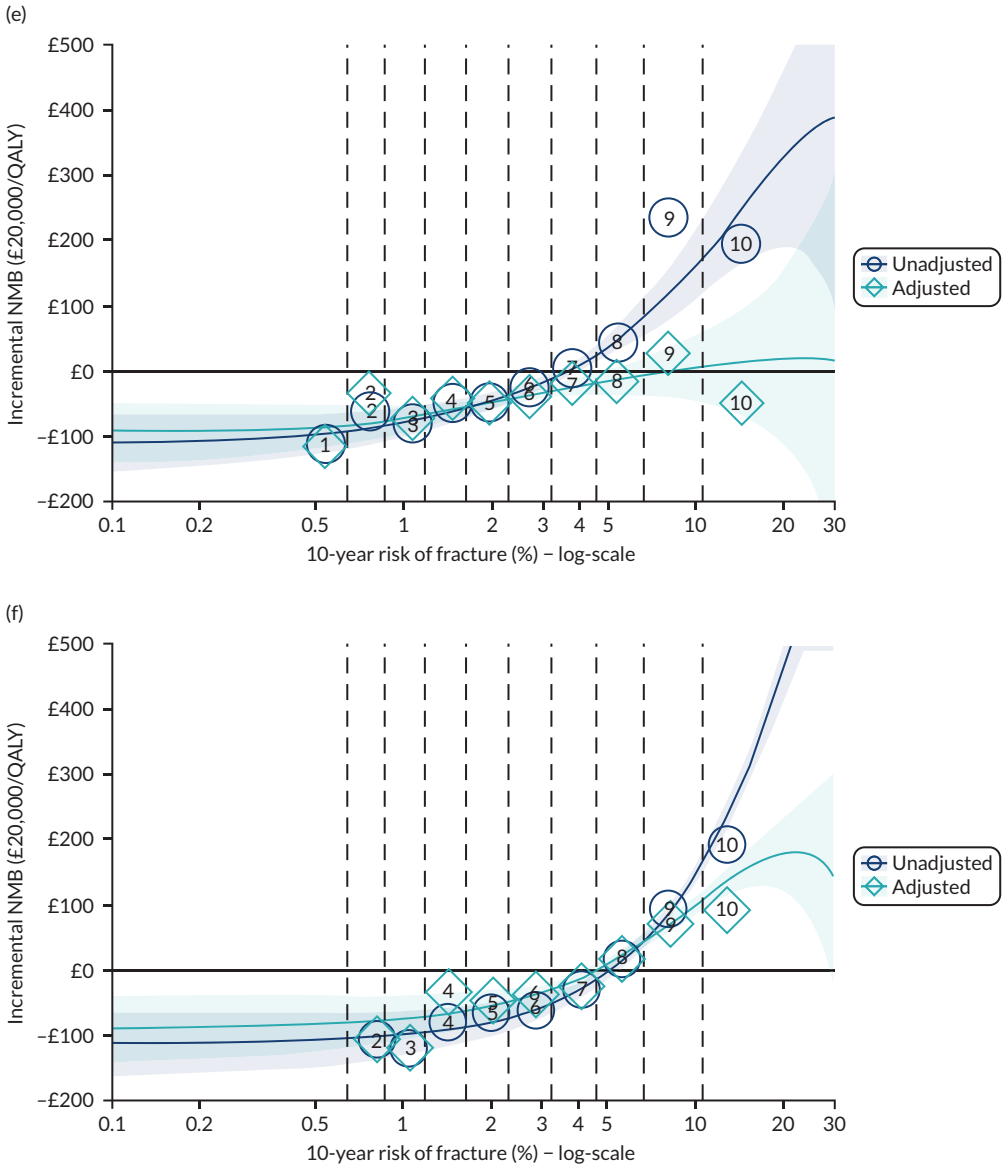

FIGURE 62 Cost-effectiveness of bisphosphonates (incremental net monetary benefit compared with no treatment) as a function of age, sex and risk of fracture, with different assumptions about competing risk of non-fracture death. (a) Men aged 50 years; (b) women aged 50 years; (c) men aged 60 years; (d) women aged 60 years; (e) men aged 70 years; (f) women aged 70 years; (g) men aged 80 years; and (h) women aged 80 years. GAM fitted to model outputs comprising 5 million simulated patients. Lines show fitted model prediction, shaded areas show 95% CI, vertical dashed bars represent deciles of risk and numbered shapes show mean values for people within each tenth of the population (where these are missing, fewer than 100 of the total 5 million simulated people fell into the group). (*continued*)

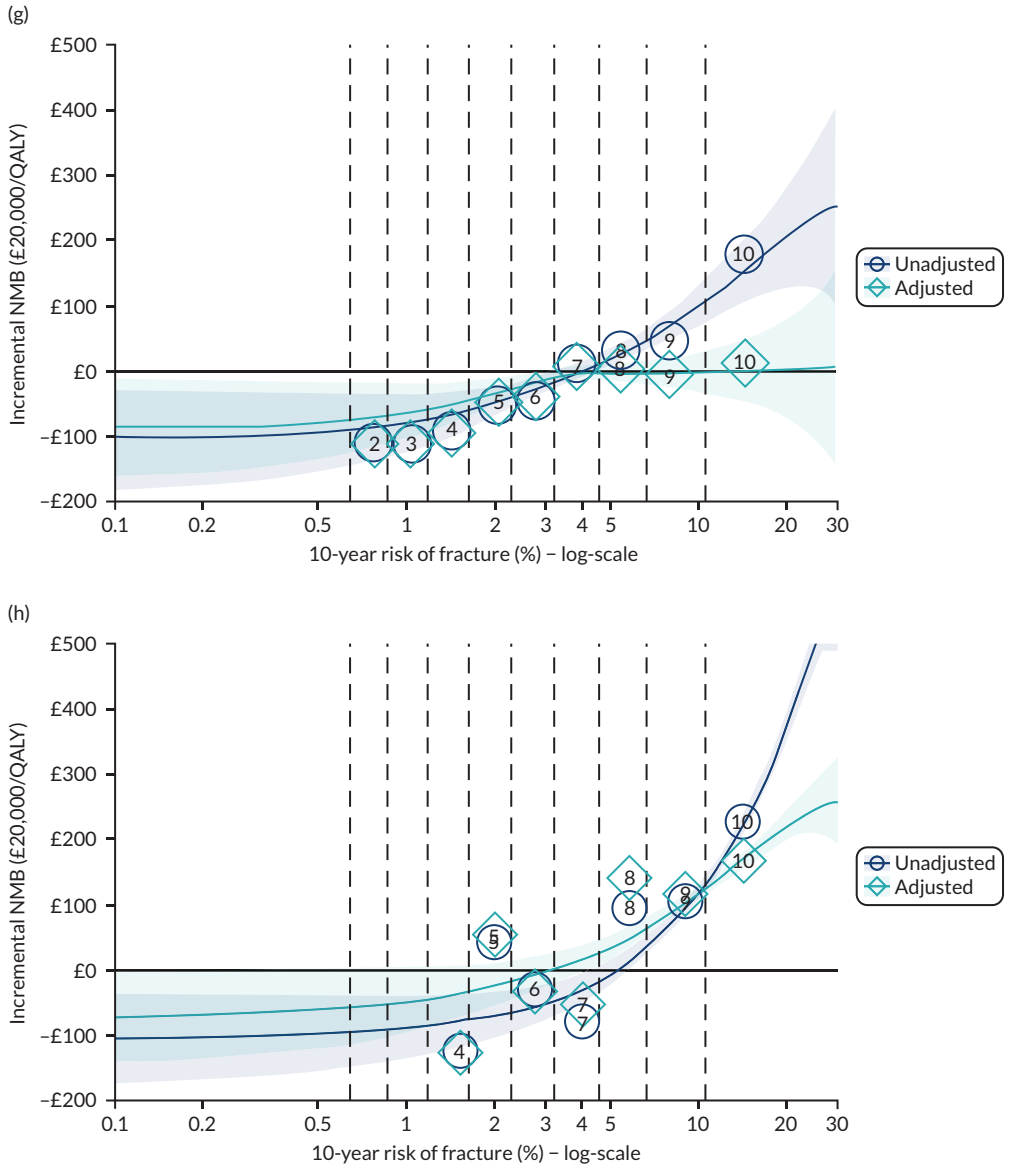

FIGURE 62 Cost-effectiveness of bisphosphonates (incremental net monetary benefit compared with no treatment) as a function of age, sex and risk of fracture, with different assumptions about competing risk of non-fracture death. (a) Men aged 50 years; (b) women aged 50 years; (c) men aged 60 years; (d) women aged 60 years; (e) men aged 70 years; (f) women aged 70 years; (g) men aged 80 years; and (h) women aged 80 years. GAM fitted to model outputs comprising 5 million simulated patients. Lines show fitted model prediction, shaded areas show 95% CI, vertical dashed bars represent deciles of risk and numbered shapes show mean values for people within each tenth of the population (where these are missing, fewer than 100 of the total 5 million simulated people fell into the group).

TABLE 59 Outputs of GAM, adjusting for age, sex and fracture risk: threshold at which alendronate becomes cost-effective compared with no treatment

	Unadjusted				Adjusted			
	Men		Women		Men		Women	
Age (Years)	Threshold	95% CI	Threshold	95% CI	Threshold	95% CI	Threshold	95% CI
40	5.1	3.6 to inf[a]	4.6	3.5 to 7.2	inf[a]	5.5 to inf[a]	7.6	4.3 to inf[a]
50	4.3	3.5 to 6.1	5	4.3 to 6.4	inf[a]	5.5 to inf[a]	7.7	5.2 to inf[a]
60	4	3.4 to 4.7	5.4	5 to 6.1	9.2	5.4 to inf[a]	7.8	6.2 to 16
70	3.8	3.4 to 4.3	5.1	4.7 to 5.4	8.8	5.2 to inf[a]	4.5	3.9 to 5
80	4	3.4 to 4.6	5.2	0 to 5.9	6.6	3.6 to inf[a]	3.5	0 to 4.6
90	5.8	0 to 8.7	12	0 to 14	3.5	0 to 13	0.1	0 to 11

a There is no level of risk at which the intervention would become cost-effective.

EME
HSDR
HTA
PGfAR
PHR

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