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Supplementary Appendices

Supplementary Material for:

Modelling the economic impact of interventions for older populations with multimorbidity: a method of linking multiple single-disease models

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Appendix 1. Justification for disease selection

The criteria used for selecting the diseases to be modelled in the case study are summarised in Box 1.

Box 1. Criteria for selecting diseases to model

- Diseases with major cost implications: High costs to the UK NHS and Personal Social Services of treating/managing the diseases
- Diseases of the elderly: Diseases with significant mortality and morbidity burden for older population and diseases whose incidence is expected to increase as population ages.
- Establishing a balance between different disease areas in order to cover a spectrum of conditions.
- Diseases that are correlated with respect to their incidence/prevalence and thus are more likely to co-occur
- Whether there are sufficiently recent HTA reports undertaken for the disease in order that a peer-reviewed model could be replicated.
- Diseases of hard endpoints, rather than those being risk factors for other diseases themselves, such as diabetes and hypertension

Diseases with significant cost implications to the UK NHS and Personal Social Services (PSS) for an ageing population were considered for inclusion in the model. Diseases expected to become more prevalent as a population ages were given a priority.

A balance between different disease areas was also considered as one of the criteria. Including diseases from one or two areas of diseases whose mechanisms are similar may be misleading in estimating the broad impact of population ageing on healthcare expenditure and the interactions between diseases. Among diseases of significant economic, mortality and morbidity burdens, a spectrum of diseases that affect different parts of the body were included.

Diseases that are potentially correlated were considered for inclusion in the case study. Seemingly unrelated health conditions may co-occur in individuals as they often share common underlying risk factors (for further details, see Appendix 2).

Fracture risks are influenced by the presence of cardiovascular disease (CVD). In a study that was a part of the Rochester Epidemiology Project, myocardial infarction (MI) was associated with higher risk of all types of osteoporotic fracture [1]. Excess fracture risks after MI were found with the overall adjusted hazard ratio (HR) of 1.32 (95% CI 1.12-1.56) across all anatomic sites.

Further, the prevalence of heart disease (HD) among Alzheimer's disease (AD) patients was considered higher than that of HD within an age- and gender-matched general population. A number of studies have found that AD often co-exists with vascular conditions such as hypertension, hyper-cholesterolaemia, and diabetes mellitus [2-6].

Osteoporosis and stroke share several risk factors, including age, smoking, low physical activity, and hypertension. Thus, low bone mineral density (BMD) and high stroke risk can be correlated. Studies have shown that low BMD or a history of fracture has an association with the incidence of stroke [7-9]. Jørgensen et al. [9] reported that women with BMD values in the lowest quartile had a higher risk of stroke than women with BMD values in the highest quartile (odds ratio (OR)= 4.8), and a linear trend over the quartiles was statistically significant. The OR for stroke increased 1.9 per SD (0.13 g/cm^2) reduction in BMD. The association between low BMD and stroke in women remained significant when the analysis was adjusted for potential confounders. In men, however, no statistically significant difference in BMD between the stroke patients and their controls was found.

The presence of recently published (or in press) NIHR HTA reports was considered as it was deemed as evidence of the importance of the disease to major stakeholders such as decision-makers in local government, policy-makers (including the National Institute for Health and Care Excellence (NICE)), health professionals, and the general public. Further, the model structures reported in the HTA reports were largely replicated.

Diseases with hard endpoints were preferred to those which were surrogate risk factors for other diseases. It was believed that such diseases could be embedded as a risk factor, and the consequences of the diseases could be represented in the models of other diseases.

Using the selection criteria, the three diseases with significant mortality and disability burdens for the elderly – heart disease (including stroke and MI), Alzheimer's disease, and osteoporosis – were chosen for the case study.

The most expensive disease category was cardiovascular disease. Heart conditions, such as coronary heart disease (CHD) and MI, and stroke were selected for modelling as they account for the largest

proportion of mortality and prevalent cases in cardiovascular disease among older individuals [10], and impose significant economic burden on the overall healthcare system [11].

Dementia was selected for modelling considering its cost, potential association with CVD, the balance between the chosen diseases, and likely impact of population ageing. Amongst brain disorders, dementia was the most expensive category of spending [12], and affects older people in particular with the incidence positively correlated with age [13]. Only the most common form of dementia, Alzheimer's disease (AD), was modelled in this study as the current NICE guidance and relevant model-based studies (including HTA reports) focussed on AD.

It was considered appropriate to include one or more musculoskeletal disorders due to the increasing prevalence and incidence with age. Amongst the musculoskeletal conditions, osteoporosis was deemed appropriate to include in the model due to its high cost. Osteoarthritis (OA) was not selected as previous models have been built for OAs at different anatomical sites such as knees, hips, and joints of hands, which make OA more difficult to include given the aim of this paper. Furthermore, the incidence of OA is difficult to estimate as the onset is not well-defined due to the discrepancy between the symptomatic OA and OA based on the radiological changes. Rheumatoid arthritis (RA) was considered for inclusion as RA mainly affects people aged 65 years and older [14]. However, RA was not chosen for the modelling given that the cost of RA did not exceed that of OA and chronic obstructive pulmonary disease.

Appendix 2. Incorporating correlations between diseases

The following correlations were incorporated in the proof-of-concept model.

1) Prevalence of AD for people with and without HD
2) Incidence of AD for people with and without HD
3) Incidence of hip fracture for people with and without a history of MI
4) Stroke risks among people with and without a history of hip fracture
5) Incidence of AD with and without low BMD

AD=Alzheimer's disease; HD= heart disease; MI= myocardial infarction; BMD=bone mineral density

This section describes only the correlations between the prevalence of HD and AD ((1) in above table) and the incidence of osteoporotic fracture and the presence of HD ((3) in above) incorporated in the linked model and how these correlations were implemented. The correlations 1)-5) were selected due to the data availability. Different incidence and prevalence estimates were applied to two groups of people with and without the other underlying condition. Similar calculation methods to those described in this section were applied to other correlations.

Targeted literature searches in the Medline and/or EMBASE databases using a combination of the disease names were conducted to identify the required data on correlations between the modelled diseases. Wherever possible, data on the incidence and prevalence of one disease with and without the other diseases was obtained. Further details on the correlations 2), 4) and 5) can be found in Youn (2016) [15].

Correlation between Heart disease and Alzheimer's disease

Systematic searches for literature reporting the prevalence of AD and other co-existing conditions and the outcomes of intervention for patients with AD and other relevant conditions were conducted within the Medline and EMBASE databases. However, very few papers that could provide numerical data for populating the model were identified.

A small number of studies that discussed empirical data on the effect of one disease on another were identified. As Maslow [2] noted, studies mainly listed common co-existing conditions that were

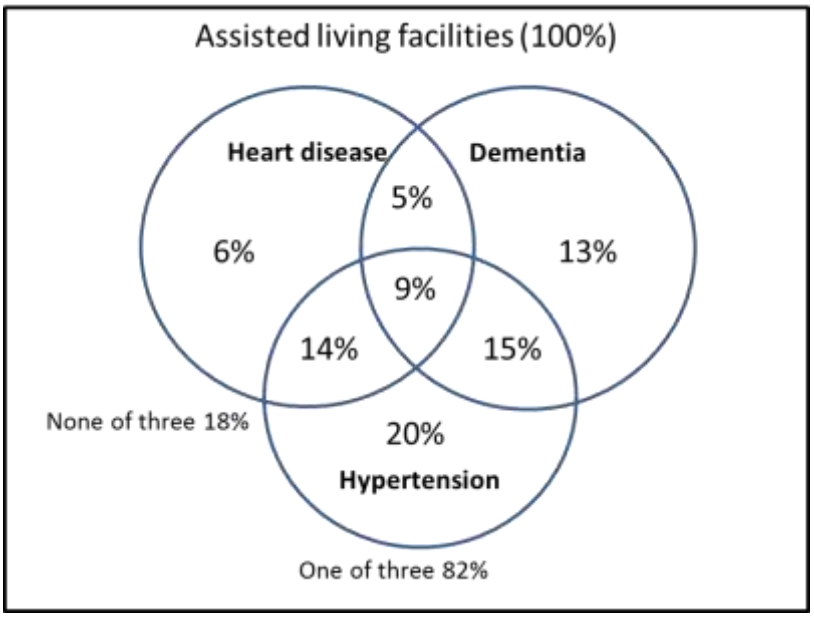
present in their study population only, or intentionally excluded people with AD who have other co-morbidities as the effect of other diseases could confound the effect of AD. Studies focussing on heart disease reported similar results.

Correlation of prevalence

The prevalence of HD among AD patients was considered higher than that of HD within an age- and gender-matched general population. A number of studies have found that AD often co-exists with vascular conditions such as hypertension, hyper-cholesterolaemia, and diabetes mellitus [2-6].

For instance, the US National Center for Health Statistics survey found that 82% of people in assisted living facilities where help is provided for daily activities such as bathing and dressing had one or more of dementia, hypertension, and heart disease (Figure S2.1) [16]. 42% of the residents had Alzheimer's disease or other forms of dementia and 34% had heart disease. 14% of people had both dementia and heart disease and 9% of them had all three of the diseases. However, as this survey was conducted in assisted living centres, the survey respondents were likely to be older than other study populations.

Figure S2.1. Co-morbidities of residents in assisted living facilities



Source: The National Center for Health Statistics, 2010 [16]

In order to incorporate the linkages between AD and HD, those with and without HD had different prevalence of AD: the total proportion of people who have AD was divided into the proportion of AD patients among people with heart disease and the proportion among people without HD.

For each age and sex group, the total prevalence of AD, $P(AD = 1)$, can be seen as a weighted average of two conditional probabilities $P(AD = 1|HD = 1)$ and $P(AD = 1|HD = 0)$ as follows;

$$P(AD = 1) = P(AD = 1|HD = 1) \cdot P(HD = 1) + P(AD = 1|HD = 0) \cdot P(HD = 0)$$

[Eq. 1]

where AD and HD are binary variables taking the value of one when the disease is present and zero otherwise. Therefore, $P(AD = 1)$ and $P(HD = 1)$ are the prevalence of AD and HD, respectively. $P(AD = 1|HD = 1)$ denotes the probability of having AD conditional on the presence of HD, or the prevalence of AD among those with HD, and $P(HD = 1|AD = 1)$ the prevalence of HD among those with AD.

In the same way, the total prevalence of heart disease can be calculated as:

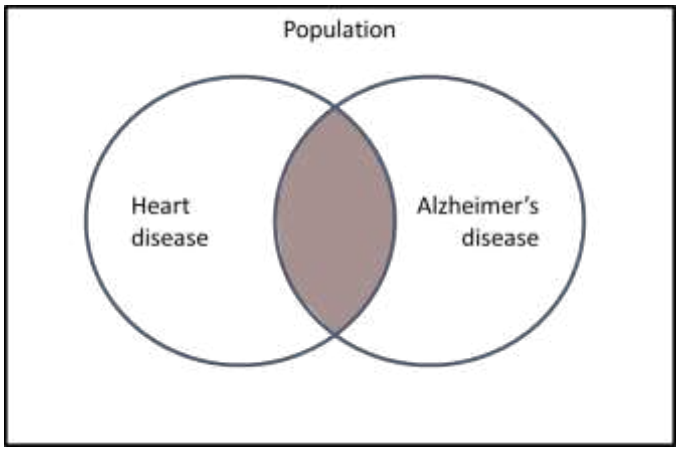
$$P(HD = 1) = P(HD = 1|AD = 1) \cdot P(AD = 1) + P(HD = 1|AD = 0) \cdot P(AD = 0)$$

[Eq. 2]

Eq. 2 expresses the total prevalence of HD in terms of $P(HD = 1|AD = 1)$ and $P(HD = 1|AD = 0)$ using the value of AD prevalence, $P(AD = 1)$. Regardless of which equation to use, the split should

be the same as $P(HD = 1|AD = 1)$ and $P(AD = 1|HD = 1)$ represent the same coloured area in Figure S2.2 although the actual figures of the conditional probabilities differ depending on which disease status is assumed to be known.

Figure S2.2. Prevalence linkage between AD and heart disease



However, Eq. 2 could not be used as the total prevalence of heart disease had to be partitioned among the cardiac events included in the model and data required for using Eq. 2 were not available from the literature searches. Hence, the prevalence of AD was divided into the prevalence of AD for people with and without HD using Eq. 1.

Using Bayes' theorem, $P(AD = 1|HD = 1)$ in Eq. 1 was calculated as $P(AD = 1|HD = 1) = \frac{[P(HD=1|AD=1)\cdot P(AD=1)]}{P(HD=1)}$ **[Eq. 3]**. The relationship in Eq. 1 was used to calculate $P(AD = 1|HD = 0)$. The following sections describe the methodology and report the calculation results.

Calculation and calibration of the prevalence of Alzheimer's disease among heart disease patients

The prevalence of AD among people with HD, $P(AD = 1|HD = 1)$, was calculated by combining the results on $P(HD = 1|AD = 1)$ and $P(HD = 1)$ using Eq. 3. Subsequently, the prevalence of AD among people without HD, $P(AD = 1|HD = 0)$, was also estimated using Eq. 1.

The resulting prevalence of AD divided into $P(AD = 1|HD = 1)$ and $P(AD = 1|HD = 0)$ is shown in Table S2.1. These values were used in the linked model as the prevalence of AD in relation to the

presence of heart disease. The ratio $\frac{P(AD=1|HD=1)}{P(AD=1|HD=0)}$ varied with age group and sex as the prevalence of individual diseases, $P(HD=1)$ and $P(AD=1)$, differ between age and sex.

Table S2.1. Prevalence of AD divided into the prevalence for people with HD and that for people without HD (before calibration)

	Prevalence of AD					
	People with HD ①		*People without HD* ②		*Ratio* (①/②)	
Age	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
<65	0	0	0	0	NA	NA
65-69	0.018267	0.044718	0.006785	0.005929	2.69	7.54
70-74	0.036962	0.05099	0.015618	0.009068	2.37	5.62
75-79	0.051255	0.091056	0.032751	0.034654	1.57	2.63
80-84	0.095646	0.180764	0.058681	0.068831	1.63	2.63
85+	0.196727	0.363585	0.108037	0.132586	1.82	2.74

The prevalence of AD before and after applying the correlations were compared using the values sampled at the model entry in order to see whether the estimation method used for splitting prevalence produced similar results. The total prevalence of AD and the prevalence for people with and without HD are compared in Table S2.2. The prevalence values of AD with and without HD were combined for comparison with the total AD prevalence before splitting using 100,000 simulated individuals for each age group (in order to have enough numbers of simulated individuals in each age group). The absolute percentage differences ranged from 0.23% to 5.09% between the total population values and the split values of prevalence. The percentage difference was the largest for female population aged 70-74 years. The differences could be due to the use of the single estimate of $P(HD = 1|AD = 1)$ in Eq. 3 for all age groups and sex, which fails to reflect variation among different populations in the estimation equation.

Although the differences could be considered small, the prevalence of AD split for people with and without HD was calibrated to match the total prevalence. Calibration was performed in order to start the model with the same population with respect to the total prevalence of AD. Based on the total prevalence values, age- and sex-specific calibration multipliers were applied to the prevalence values for people with and without HD. These were calculated as the total prevalence divided by the combined prevalence using split values. The calibrated prevalence after these multipliers were applied was used in all models for this paper where AD and heart disease were correlated.

Table S2.2. Comparison of simulated proportions of people with Alzheimer's disease (AD): between when the total prevalence of AD was used and when the prevalence of AD split into HD and non-HD groups was used

	Total prevalence of AD (before splitting)		**Combined prevalence of AD using split prevalence values***		**% Difference (compared with the total prevalence AD)**	
Age	Men	Women	Men	Women	Men	Women
<65	0	0	0	0	0	0
65-69	0.0101	0.0108	**0.0098**	**0.0104**	-3.01%	-3.98%
70-74	0.0223	0.0158	**0.0232**	**0.0166**	3.88%	5.09%
75-79	0.0403	0.0511	**0.0387**	**0.0503**	-3.94%	-1.52%
80-84	0.0734	0.1015	**0.0732**	**0.1020**	-0.38%	0.44%
85+	0.1411	0.1980	**0.1451**	**0.1985**	2.79%	0.23%

*Based on the results of 100,000 simulated individuals for each age group.

In order to examine the effect of the calibration at the population level, the numbers of people with AD across all age groups in the models before and after calibration were compared in Table S2.3 when 200,000 individuals aged 65 years and over were simulated for each model (the age distribution for people aged 65 and over was adapted from the ONS mid-2012 UK population estimates). The total numbers of people with AD among 200,000 simulated individuals from models with and without calibrated prevalence values were compared with that from the model where heart disease and AD were independently linked. The calibration reduced the difference between when the total AD prevalence was applied and when the split prevalence values were used from 0.50% to 0.24% for male population and from 1.89% to 1.18% for females.

There still existed differences in the number of people with AD after calibration due to Monte Carlo sampling error. Perfect calibration would have been possible if the calibration factors were calculated using the model results with the infinite number of runs for each age and sex group. In addition, if the infinite number of individuals were simulated in the perfectly calibrated model and the independently linked model for figures in Table S2.3, the differences would have been eliminated.

Table S2.3. Number of individuals with Alzheimer's disease (AD) before and after calibration compared with when total prevalence without correlations was applied

Number with AD when Total AD prevalence was used**		**Number with AD when split prevalence values were used* (difference (n; %))**			
Men	Women	Men	Women	Men	Women
		Before calibration		**After calibration**	
3378	6292	3395 (+17; +0.50%)	6411 (+119; 1.89%)	3386 (+8; 0.24%)	6366 (+74; +1.18%)

*Among 200,000 simulated individuals aged 65 years and older; **Results from the model where heart disease and AD were linked with independence between diseases assumed.

Correlation between Heart disease and Osteoporosis

The model in this study focussed specifically on correlations regarding hip fracture, and MI and stroke as these events are associated with the highest costs and utility effects. This section describes the correlation between hip fracture and a history of MI. Similar calculation was performed for the correlation between the risk of stroke and a history of hip fracture.

Incidence of hip fracture and prevalent cardiovascular disease

Fracture risks are influenced by the presence of CVD. In a study by Gerber and colleagues [1], MI was associated with higher risk of all types of osteoporotic fracture. Excess fracture risks after MI were found with the overall adjusted hazard ratio (HR) of 1.32 (95% CI 1.12-1.56) across all anatomic sites. Trends of the fracture incidence rates for three time-periods (1979-1989; 1990-1999; 2000-2006) were tested and an increase in fracture rates over time was found among MI patients. An HR of 1.66 for both men and women for hip fracture was used in the model, which was for the most recent time period (2000-2006). Data reported in Gerber et al. [1] was used in the model as this study was based on a large sample size and similar ethnic group to that of the UK, and provided relatively recent data in the format suitable to be applied to the time-to-event distributions used in the model. Only a transient increase of fracture risks after MI was identified in the study. In the Gerber et al. (2011) study, as the mean follow-up time was only 4 years and the association between and MI and 5-year risk of osteoporotic fracture was reported, HR was applied for five years after MI.

The incidence of hip fracture was split between that for those with MI and that for those without. Using the prevalence estimates of MI used to populate the individual heart disease model, the total incidence of hip fracture was split between the incidence of hip fracture for patient who had an MI within 5 years and that for patients who did not have MI for the last 5 years. These were reported in Table S2.4 for those on no treatment (A) and on drug treatment for osteoporosis (B) where an RR of 72% for hip fracture was applied [17]. Due to the low prevalence of MI among younger age groups, the baseline incidence for those without MI was similar to the total incidence including both groups with and without MI.

Table S2.4. Hip fracture incidence split between rates for those with MI and without MI

A. Hip fracture incidence with and without MI – No drug treatment

	Total incidence of hip fracture		Baseline rate r (without MI)		Rate for patients with MI	
Age	Men	Women	Men	Women	Men	Women
45-50	0.00030	0.00020	0.00030	0.00020	0.00049	0.00033
50-55	0.00030	0.00020	0.00030	0.00020	0.00049	0.00033
55-60	0.00070	0.00050	0.00067	0.00049	0.00112	0.00082
60-65	0.00030	0.00080	0.00029	0.00079	0.00048	0.00131
65-70	0.00080	0.00130	0.00073	0.00127	0.00121	0.00211
70-75	0.00110	0.00210	0.00100	0.00206	0.00167	0.00341
75-80	0.00200	0.00420	0.00180	0.00396	0.00299	0.00658
80-85	0.0068	0.0097	0.00613	0.00915	0.01017	0.01519
85+	0.0099	0.0217	0.00892	0.02047	0.01481	0.03398

B. Hip fracture incidence with and without MI – For individuals on drug treatment for osteoporosis

	Total incidence of hip fracture – on drug treatment		Baseline rate r (without MI)		Rate for patients with MI	
Age	Men	Women	Men	Women	Men	Women
45-50	0.00025	0.00018	0.00025	0.00017	0.00041	0.00029
50-55	0.00024	0.00017	0.00024	0.00017	0.00040	0.00028
55-60	0.00050	0.00033	0.00048	0.00032	0.00080	0.00054
60-65	0.00020	0.00055	0.00019	0.00054	0.00032	0.00090
65-70	0.00060	0.00092	0.00054	0.00090	0.00090	0.00149
70-75	0.00081	0.00150	0.00074	0.00147	0.00123	0.00244
75-80	0.00145	0.00303	0.00131	0.00286	0.00217	0.00475
80-85	0.00490	0.00695	0.00442	0.00656	0.00733	0.01088
85+	0.00713	0.01557	0.00643	0.01469	0.01067	0.02439

The incidence rates of hip fracture with and without a recent MI reported in Table S2.4 were used as the baseline event rates for hip fracture for the first 5 year period after MI. The relative risks associated with factors that can influence the event rates, such as low BMD and previous fracture, were applied onto these baseline rates. When sampling time to next hip fracture, these baseline incidence rates of hip fracture were updated when the sampled time to event was longer than the time before a change in age band, or the time left to a change in the drug efficacy due to the

treatment fall time after discontinuation. Hence, all three time intervals for which different event rates are applied – time to 5 years after MI, time to next age band, and time to next efficacy change due to the fall time of treatment effect – were continuously compared with the sampled time to event (TTE) value. When the sampled TTE value is longer than any of the three, the baseline incidence rates were changed accordingly and TTE was resampled.

Appendix 3. Parameter estimates and data sources

Event Rates

This section describes the event rates used for the base-case model only for HD due to the addition of PAD and updated parameters. Parameter estimates used in the AD and osteoporosis models were based on the data reported in the HTA reports [13, 17] and are detailed in Youn [15]. The data sources were identified from the six UK-based studies [18-23]. The most appropriate parameter estimates reported for similar populations and contexts in the six studies and their sources of data were used for the model in this research. UK-sourced data were used wherever possible, and age-dependent time-variant rates of transitions between health events were preferred.

All included HD disease states except PAD were split into two temporal categories – first year and subsequent years after the event – due to the difference in the rates for transitions to other events, costs, and/or utility weights between the first year of the event and thereafter. Various sources for cardiac death rates were used dependent on the 'from' state of the transition. The rate of transition to cardiac death varied with the age group and the temporal period (first year or subsequent years after the event), and time to cardiac death was sampled from an exponential distribution, the parameter of which produced the appropriate rate.

The event rates used in the model are summarised in the next sections by the origin of transitions, with each section followed by a summary table of the estimates. In addition, rates of transitions to fatal stroke and PAD were described in separate sections as they applied regardless of the origin of transitions.

Transitions from event-free state (at model initiation)

Event rates differed depending on whether an individual is on primary or secondary prevention interventions, or is untreated. Rates of transitions from the event-free state are summarised in Table S3.1.

Table S3.1. Baseline annual rates of transition from event-free state

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimates**	**Sources**
Event free	MI	Rate for men = 0.01624; Rate for women = 0.01123	WOSCOPS (Shepherd et al. 1995 [24]) and Framingham studies (D'Agostino et al. 2008 [25])
	Stroke	Exponential mean of Exp(9.218 + (-0.064)*age at event + (-0.176)*gender) for time to event distribution $T \sim Exp(\hat{\lambda})$. Then, the prob of stroke being fatal applied. P(fatal stroke)=e^xb/[1+e^xb] where xb= -4.874 + 0.043*age – 0.074*gender.	Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) trial results [22]
	Angina	Rate = 0.0027 per patient-year.	ASCOT-LLA data [26]
	Revascularisation	For only primary and secondary prevention populations, Exponential mean of Exp(5.250 + (-0.013)*age at event + (0.479)*gender) for time to event distribution $T \sim Exp(\hat{\lambda})$. Otherwise, the national average rate of revascularisation was used.	ASCOT trial [22] National Audit of PCI [27]
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study [28]
	CVD death	For individuals not receiving any interventions, Males (females): 45-54 years 0.000639 (0.000178); 55-64 years 0.001711 (0.000573); 65-74 years 0.004275 (0.001994); 75-84 years 0.013182 (0.008621); 85 years and over 0.040947 (0.035576). For only primary and secondary prevention populations, Exponential mean of Exp(6.576 + (-0.035)*age at event + (0.437)*gender) for time to event distribution $T \sim Exp(\hat{\lambda})$.	Mortality Statistics: Deaths registered in 2012 [29] ASCOT trial [22]

Transitions from MI

Table S3.2. Baseline annual rates of transitions from myocardial infarction

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimate**	**Sources**
MI	MI	For age groups 1-5: First (subsequent) year(s) rates: 0.13697 (0.01633), 0.12239 (0.01806), 0.10747 (0.01867), 0.09146 (0.0180), 0.07375 (0.01613).	NICE TA94 Table 52 [30]; Nottingham Heart Attack Register (NHAR) [31].
	Stroke	For age groups 1-5: First (subsequent) year(s) rates: Group 1 (< 55): 0.00150 (0.0004), Group 2 (55-65): 0.00321 (0.00100), Group 3 (65-75): 0.00682 (0.00220), Group 4 (75-85): 0.01420 (0.00471), Group 5 (> 85): 0.02819 (0.00914).	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR);
	Angina	Exponential rate = 0.05975	Ara et al. 2009. Table 8 [23]; Fox et al. 2005 [32]
	Revascularisation	First year rate = 0.504347	TNT trial [20]
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study (Leng et al. 1996)
	CVD death	For age groups 1-5: First (subsequent) year(s) rates: Group 1 (< 55): 0.01755 (0.00541), Group 2 (55-65): 0.03387 (0.00955), Group 3 (65-75): 0.06465 (0.01603), Group 4 (75-85): 0.12059 (0.02482), Group 5 (> 85): 0.21791 (0.03615).	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR) [31].

Transitions from Stroke

Table S3.3. Baseline annual rates of transitions from Stroke

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimate**	**Sources**
Stroke	MI	Rates by age group: Group 1 (< 55): 0.00160, Group 2 (55-65): 0.00310, Group 3 (65-75): 0.00552, Group 4 (75-85): 0.00803, Group 5 (> 85): 0.01045.	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR) [31].
	Stroke (Stroke recurrence)	Baseline rates for 0-1, 1-5, 5-10 years for individuals aged <65: 0-1 year rate= 0.06401 (mean = 15.6237); 1-5 year rate= 0.02694; 5-10 year rate= 0.01887. Then, probability of stroke being fatal= e^xb/[1+e^xb], where xb= -4.874 + 0.043*age – 0.074*gender, was applied.	Mohan et al. 2009 [33] – Stroke recurrence; ASCOT trial [22]
	Angina	Rate = 0.0027	Assumed the same as the rate of transition from event free to angina state (NICE TA 94 Table 52)
	Revascularisation	Rate= 0.01056	TNT trial [20]
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study [28]
	CVD death	For age groups 1-5: First (subsequent) year(s) rates: Group 1 (< 55): 0.00924 (0.00421), Group 2 (55-65): 0.02245 (0.00985), Group 3 (65-75): 0.05340 (0.02102), Group 4 (75-85): 0.12466 (0.04207), Group 5 (> 85): 0.27839 (0.07796).	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR) [31]

Transitions to Fatal Stroke

If the reported data did not explicitly state that the event probabilities were for non-fatal stroke only, then a proportion of the patients who experience a stroke was assumed to die due to the stroke. The proportion of fatal stroke among all stroke events was estimated using the logistic regression equation reported in the ASCOT trial results [22] with an exception of transitions from revascularisation state where a 50% probability of stroke being fatal was assumed as in Ara et al. (2009). Thus, the transitions to stroke from event free, stroke, angina and revascularisation states included a subset of patients having a fatal event and subsequently moving to cardiac death state.

Transitions from Angina

Rates of transitions from angina are given in Table S3.4. Individuals were assumed to have stable angina first and then progress to unstable angina, which requires more intense medical treatments. Once unstable angina was developed, it was assumed that patients could not improve to stable angina.

Table S3.4. Baseline annual rates of transitions from angina

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimates**	**Sources**
Angina	MI	1) From Stable angina: Rate = 0.01520; 2) Unstable angina 5%, 4.9%, 4.7%, 4.3% from 1st year event. 3.5%, 6.3%, 11.2%, 18.5% from subsequent yrs event for those aged <55, 55-65, 65-75, 75-85 yrs, respectively.	Juul-Moller, Edvardsson [34]; Ara, Pandor [23], Table 8; Gray and Hampton [31];
	Stroke	1) From Stable angina: Rate = 0.00791; Then, the prob of stroke being fatal applied, probability = e^xb/[1+e^xb], where xb= -4.874 + 0.043*age – 0.074*gender. 2) From Unstable angina: For age groups of <65, <75, <85, >85 years, [1st year rate] To non-fatal stroke: 0.2%, 0.5%, 1%, 2%; To fatal stroke: 2.6%, 4.3%, 7%, 10.3%; [subsequent yrs rate] To non-fatal stroke: 0.1%, 0.1%, 0.3%, 0.7%; → Fatal stroke: 0.4%, 0.5%, 0.6%, 0.7%.	1) Juul-Moller, Edvardsson [34]; NICE [30]; Lindgren, Buxton [22] 2) Ara et al. 2009 (HTA) Table 8.; Gray and Hampton [31]
	Angina (unstable)	Annual probability from stable angina to unstable angina: Group 1 (< 55): 0.0013, Group 2 (55-65): 0.0029, Group 3 (65-75): 0.0060, Group 4 (75-85): 0.0091, Group 5 (> 85): 0.0122.	NICE TA 94: Table 52.
	Revascularisation	Rate=0.00269	Assumed the same as the minimum revascularisation rate from PAD state. (Leng et al. 1996)
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study (Leng et al. 1996)
	CVD death	1) If no history of angina= Group 1 (< 55): 0.009, Group 2 (55-65): 0.0035, Group 3 (65-75): 0.007, Group 4 (75-85): 0.007, Group 5 (> 85): 0.007. 2) From unstable angina = (CHD and CVD death rates combined for 1st and subsequent years.	NICE TA94 (Table 52); Nottingham Heart Attack Register (NHAR).

Transitions from Revascularisation

Table S3.5. Baseline annual rates of transitions from revascularisation

Individuals not receiving statin treatment			
From State	**To State**	**Estimate**	**Sources**
Revascularisation	MI	Rate= 0.03874	Fox, Poole-Wilson [32]; Ara et al. (2009) [23]
	Stroke	Rate=0.002 with 50% of stroke being assumed to be fatal.	Henderson, Pocock [35]; Ara et al. (2009) [23]
	Angina	Rate = 0.032523	Henderson et al. (2003); Ara et al. (2009) [23]
	Revascularisation	First-year rate of having a 2nd revascularisation= 0.14491	TNT trial [20]
	PAD	Rate= 0.021149= the incidence of PAD with intermittent claudication.	Edinburgh Artery Study [28]
	CVD death	Rate = 0.005785	RITA-2 trial [35]

Transitions from PAD

Table S3.6. Baseline rates of transitions from peripheral arterial disease

Baseline rates for individuals not receiving statin treatment			
From	**To**	**Estimate**	**Sources**
PAD	MI	Rate = 0.01711	Edinburgh Artery Study [28]
	Stroke	Rate= 0.01408	Edinburgh Artery Study [28]
	Angina	Rate= 0.02019	Edinburgh Artery Study [28]
	Revascularisation	Rate=0.00269	Edinburgh Artery Study [28]
	PAD	Rate=0	Assumed
	CVD death	Exponential mean of Exp(6.576 + (-0.035)*age at event + (0.437)*gender) for time to event distribution $T \sim Exp(\hat{\lambda})$.	The same rate as the transition from event free to CVD death: ASCOT trial [22]

Transitions to PAD

The incidence of PAD reported in the Edinburgh Artery Study was used for the estimation of transition rates to PAD. The incidence of symptomatic PAD (i.e. with intermittent claudication, IC) in general population aged 55 and over was used for all transitions to PAD event due to the lack of published evidence [28]. Age dependent incidence was not included as it was not statistically significant in the Edinburgh Artery Study [28]. However, there was some evidence of an increase with age in earlier longitudinal studies [36, 37].

Among patients with PAD, approximately 20% progress to develop severe symptoms with critical limb ischaemia (CLI) over a 5-year period and 1-2% undergo amputation over a lifetime [38]. In the model, 20% of people with IC were randomly sampled to develop CLI at the time of developing PAD for simplicity, to whom higher costs and lower utility weights were applied.

Effectiveness of statin treatments

Statin interventions was assumed to reduce the risks of coronary events (MI, angina, and fatal CHD events) and stroke. The model assumes that a proportion of individuals entering the model are receiving a statin intervention for primary and secondary prevention of CVD events. The relative risks (RRs) of events associated with statin use were applied to the baseline risks converted from the event rates reported in Tables S3.1-S3.6, and are shown in Table S3.7.

Table S3.7. Relative risks associated with statin use compared with placebo

Transitions to	Relative Risk	Source
MI	0.656	Ward et al. (2006) [18]
Non fatal stroke	0.754	Ara et al. (2009): Simvastatin 40mg/day
Fatal stroke (from Angina state)	0.876	Ara et al. (2009): Simvastatin 40mg/day
Stable Angina (from event free state)	0.59	Ward et al. (2006) [18]
To Fatal CHD event (CVD death)	0.74	Ward et al. (2006) [18]
Non CVD death (from event free state)	0.656	Ward et al. (2006) [18]

Non-disease mortality

Non-cardiac mortality rates used to construct distribution profiles for time to non-disease death were calculated by subtracting cardiac mortality rates from the all-cause death probability profiles. Cardiac mortality rates were estimated by combining the rates reported for heart disease (ICD-10 code I00-I52) and stroke (I64) using data obtained from the Mortality Statistics: Deaths registered in 2012 [29]. Cardiac mortality rates used to calculate the non-disease mortality are shown in Table S3.8. These were the same rates used for transitions to cardiac death from event-free state.

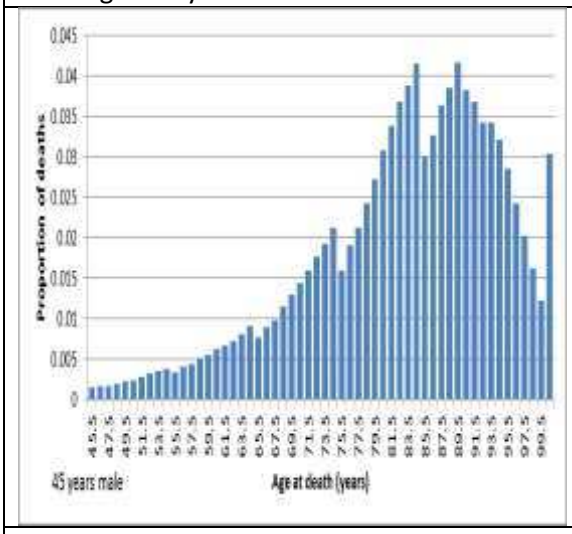
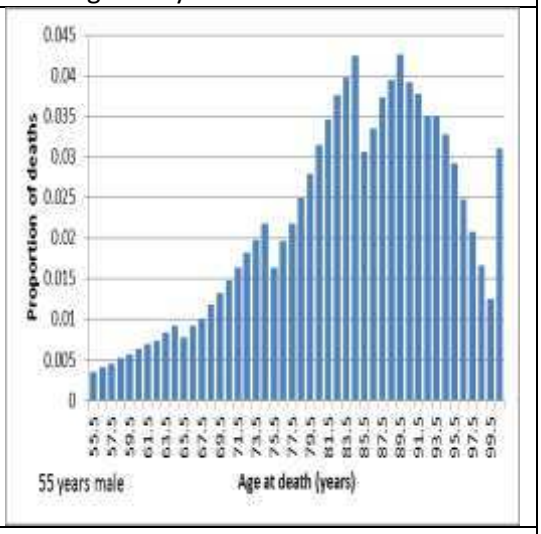
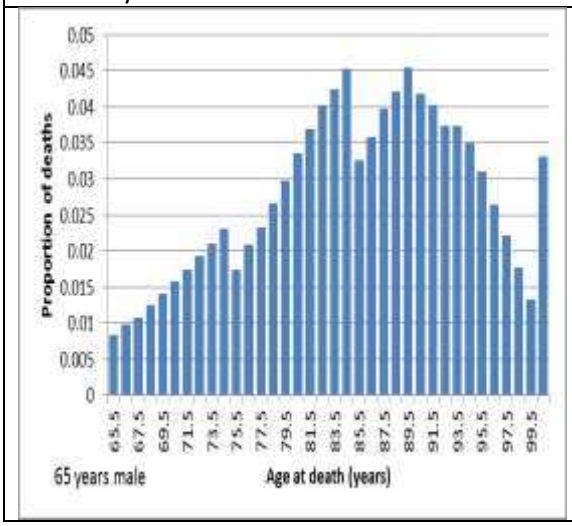
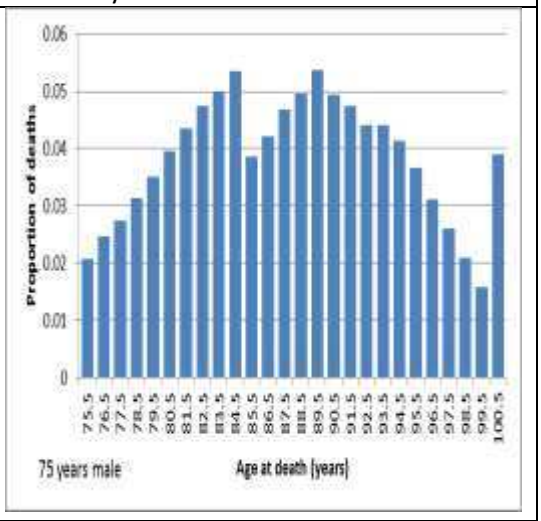
Figure S3.1 shows distributions for time to non-cardiac death for a few selected age groups. As the cardiac death rates were assumed constant across the 10-year age bands whilst the all-cause mortality rates were specified at every age x between 45 and 100 years, the probability profiles created were not smooth, but had a few stepped decreases at the age cut off values.

Table S3.8. Cardiac death rates used to estimate non-cardiac mortality rates*

	Age group				
Sex	45-54	55-64	65-74	75-84	85 and over
Male	**0.000639**	**0.001711**	**0.004275**	**0.013182**	**0.040947**
Female	**0.000178**	**0.000573**	**0.001994**	**0.008621**	**0.035576**

*Adapted from Table 8 in Deaths registered in England and Wales, 2012 [29]

Figure S3.1. Illustration of distributions for time to non-cardiac death

Male aged 45 years	Male aged 55 years
	
Male aged 65 years	**Male aged 75 years**
	

Costs

Table S3.9. Cost estimates used in the base-case model

Event	**Data within source**	**Price year**	**Estimates** [39] **(2011/2012 price)**	**Original Source**
MI - 1st year	£3,996	2007	£ 4,519.10	Ara et al. (2009) estimated using British National Formulary (2008) [40]
MI - subsequent year	£171	2004	£ 214.89	NICE TA 94 (GP contacts + medication costs)
Stroke - 1st year	£8,066	2007	£ 9,121.88	Ward, Lloyd-Jones [18]
Stroke - subsequent yr	£2,266	2007	£ 2,562.63	Ward, Lloyd-Jones [18]
Stable angina	£171	2004	£ 214.89	NICE TA 94 (GP contacts + medication costs)
Documented angina	£ 587.07	2005	£ 713.94	Taylor et al. (2009)
Revascularisation - 1st yr	£ 5,857	2007	£ 6,623.71	Taylor et al. (2009); HRG
PAD (IC)	£180	2009-2010	£189.31	Kearns, Michaels [41]
PAD (CLI)	£624	2009-2010	£656.29	Kearns, Michaels [41]; National Clinical Guideline Centre [38]
Statin treatment	£144.12	2014	£144.12	British National Formulary (2014); Estimated using the method by Ward et al. (2006)

Utilities

Baseline utility values by age and gender in the UK general population were estimated from a statistical model reported in Ara and Brazier [42].

The utility values associated with the health states included in the model were obtained from NICE TA94 and the HTA report by Ara et al. (2009). Table S3.10 describes the original sources of these

values. All the utilities were estimated using the EQ-5D, and were assumed to be multiplicative. Utility multiplier values were assumed to increase by 10% after the first year of the event as assumed in Ara et al. (2009). It was assumed that the history of revascularisation procedure did not affect the utility level, and the utility decrement for stable angina was used for individuals with history of angina. As a base-case, deterministic values for utility multipliers were used.

Alongside the current event, the history of the other health events was incorporated in the utility multiplier. For example, if a man aged 65 years who has just had a stroke has a history of MI, then the utility decrements for both stroke (first year multiplier for stroke: 0.629) and that for MI (subsequent-year multiplier: 0.836) were applied to the baseline utility (0.815); the utility weight for this person is thus 0.429 (i.e. 0.815*0.629*0.836).

When more than one cardiac event occurs within one year, the first-year periods of those events overlap. For the time periods overlapping, utility multipliers associated with the events were applied multiplicatively. For instance, if an individual experiences an MI at time=2.3 years and subsequently a stroke at time=2.7 years, then for time between 2.3 and 2.7 years, only the utility multiplier for the first year of MI would be applied (0.760) whilst for time between 2.7 and 3.3 years, utility multipliers associated with both first-year MI and first-year stroke would be applied (0.760*0.629=0.478). In the same way, for time between 3.3 and 3.7 years, utilities associated with subsequent years of MI and first year of stroke are used (0.836*0.629=0.526) In the model for this paper, whenever individuals reach these time points, they are directed to the 'utility cut off point' event in order to update variables related to utility multiplier.

Table S3.10. Utility multipliers by health state

State	**First year - Mean (S.E.)**	**Subsequent years -**	**Original Sources**
MI	0.760 (0.018)	0.836 (10% increase)	Goodacre, Nicholl [43]
Stroke	0.629 (0.04)	0.692 (10% increase)	Tengs and Lin [44]
(Stable) angina	0.808	0.889 (10% increase)	Melsop, Boothroyd [45]
Unstable angina	0.77	0.847 (10% increase)	Goodacre, Nicholl [43]
Revascularisation	0.78	0.858 (10% increase)	Serruys, Unger [46]
PAD IC	0.70	0.70	Kearns, Michaels [41]
PAD CLI	0.35	0.35	[Kearns, Michaels [41]]

Appendix 4. Comparison of the single-disease models in this study with the published reference models

Study	Model type (software)	Base-case Population	Intervention	Comparator(s)	Outcomes	Perspective	Time horizon/ price year	Health events included (e.g. Markov health states)	Stratified results (Yes/No)	Base-case ICER	Parameters driving ICER
Heart disease (HD)											
HD single-disease model in this paper	Discrete event simulation (Simul8)	General population aged 45 years and over	Statins	No statins	QALYs	NHS	Lifetime	MI, stable angina, unstable angina, stroke, revascularisation, PAD, CVD death, and non-CVD death	Yes – Base-case reported for the total population; and by age and gender, by prevention type	1) Secondary prevention - £1.5k – 4.0k/QALY vary by age and gender 2) Primary prevention - £2.2k-2.8k varied by age and gender	Reduced cost of statins (updated to 2012 values); Population age and sex distribution at model entry; Added event of PAD could lower ICERs compared to the results from Ward et al. (2006)
HD reference model by Ward et al. (2006) [18]	Markov model	A population with CHD or at increased risk of CHD events (annual CHD risk of 0.5%-3%)	Statins as a group	No statins	QALYs	NHS	Lifetime/ 2004 Discount rates of 6% for costs and 1.5% for health benefits	MI, stable angina, unstable angina, CHD death, TIA, stroke, and CVD death or non-CVD death	Yes – Base-case reported by prevention level, age and sex, and predicted annual CHD risk levels	Multiple base-case values 1) Secondary prevention - £10k-£17k /QALY 2) Primary prevention – at annual CHD risk of 3%, £10k-37k /QALY for men and £14k-48k /QALY for women	Results were most sensitive to the cost of statins, discount rates and the timeframe of the model; Larger incremental costs than the model in this study; ICERs sharply increased with age of the population

Alzheimer's disease (AD)											
AD model in this paper	Discrete event simulation (Simul8)	General population aged 45 years and over	Donepezil and memantine	BSC	QALYs	NHS and PSS	Lifetime	AD onset; diagnosis; pre-institutionalisation; institutionalisation; and death	Yes – results reported for two age groups aged >45 and >65 years	Donepezil and memantine therapy dominated BSC (cost saving £14 with 0.001 QALY gain)	The model results were generally comparable with those from Bond et al. (2012). Incremental QALYs from the model for this study were smaller than those from Bond et al. (2012) as the general population was modelled with the added events of the onset and diagnosis of AD.
AD reference model by Bond et al. (2012) [13]	Markov model (Microsoft Excel)	People with mild, moderate or severe AD	donepezil, galantamine, rivastigmine, for mild-to-moderate AD, and memantine, for moderate-to-severe AD	BSC	QALYs	NHS and PSS	20 years / 2009 price	pre-institutionalisation; institutionalisation; and death	Yes – by disease severity	Donepezil for mild-to-moderate AD dominated BSC; Memantime for moderate-to-severe AD: £32.1K/ QALY (increC=£405; increQ =0.013)	Results sensitive to assumptions on discontinuation rates; Costs of institutionalisation
Osteoporosis											
Osteoporosis model in this paper	Discrete event simulation (Simul8)	General population aged 45 years and	70mg alendronate taken once	No alendronate treatmen	QALYs	NHS and PSS	Lifetime	Hip fracture; vertebral fracture, wrist	Yes – by age and gender, BMD level, status of	Alendronate dominated no treatment for 75-year-old	Age, BMD level and history of previous fracture altered the incremental costs

		over	weekly	t				fracture; proximal humerus fracture; fracture-related death; non-fracture death	previous fracture	women with T-score of -3 SDs and -2.5 SDs with no previous fracture	and QALYs. However, regardless of the willingness-to-pay threshold per QALY, the alendronate is likely to be a cost-effective option for fracture prevention.
Osteoporosis reference model by Stevenson et al. (2009) [17]	Patient-level Markov model (Microsoft Excel)	Postmenopausal women aged 50 years and over	Vitamin K; alendronate; risedronate; strontium ranelate	No alendronate; next cost-effective treatment options	QALYs	NHS and PSS	10 years (the results subsequently adjusted to account for treatment benefits beyond the initial 10 years)	Hip fracture; vertebral fracture, wrist fracture; proximal humerus fracture; nursing home entry from hip fracture; breast cancer; and coronary heart disease; and non-fracture related death	Yes – by age, BMD level, and status of previous fracture	Alendronate dominated no treatment for 75-year-old women with T-score of -3 SDs with no previous fracture; £1,226/QALY for 75-year-old women with T-score of -2.5 SDs.	Age, fracture risks, BMD and history of previous fracture could alter the ICER estimates.

Appendix 5. Dealing with stochastic uncertainty around the results from the linked model

Background : Uncertainty around DES model outputs can be represented by both first-order uncertainty, defined as stochastic variability between simulated observations assuming identical parameter values, and second-order uncertainty, defined as uncertainty in the parameters of the economic model [47].

Aim: The degree of first order uncertainty in the linked model was examined in order to identify the appropriate number of simulated individuals to ensure stable model results. Stability was defined as an adoption decision being robust with sufficiently small random errors.

Method: Incremental values were computed in comparison with no treatments for all three of the diseases (heart disease, Alzheimer's disease and osteoporosis). The first-order uncertainty around the mean incremental cost and QALYs, incremental net monetary benefit (NMB) and cost per QALY gained (CPQ) was quantified for the results from the correlated linked model for the population aged 45 years and older.

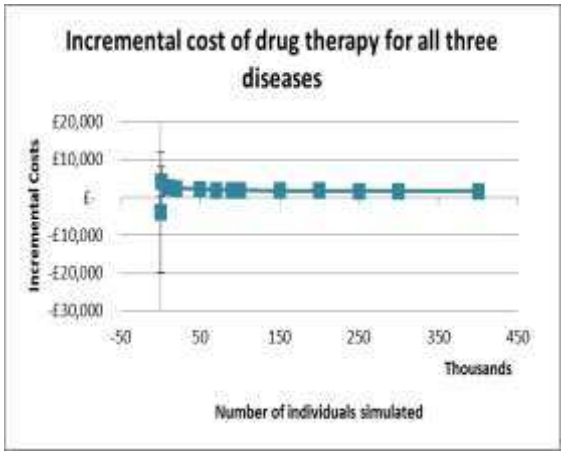
The jackknife approach was used to estimate a confidence interval for the mean cost per QALY with a reduced level of bias associated with the classical estimation of non-linear statistics [48, 49]. The standard errors of the mean results were estimated having varied the numbers of simulated individuals ranging from 1,000 to 700,000. The jackknife 95% confidence interval for the mean CPQ and the NMB results with more than 400,000 simulated individuals were derived using R programming language (R version 3.2.1, © The R Foundation) due to limited capacity of the spreadsheet software. Jackknifing execution time for the data from 700,000 simulated individuals was 4.69 hours on an Intel ® Core ™ i5 CPU 2.30 GHz processor with 4.00 GB of RAM (3.54 hours for 600,000 data points).

Results: Figure S5.1 shows that the incremental cost and QALYs stabilised when more than 200,000 individuals were simulated. The standard errors of the mean NMB and CPQ started to stabilise after running more than 500,000 simulated individuals. The chosen number of individuals to simulate was 700,000 for the base-case all-disease linked models (with and without correlations) in order to further reduce the variability of the results.

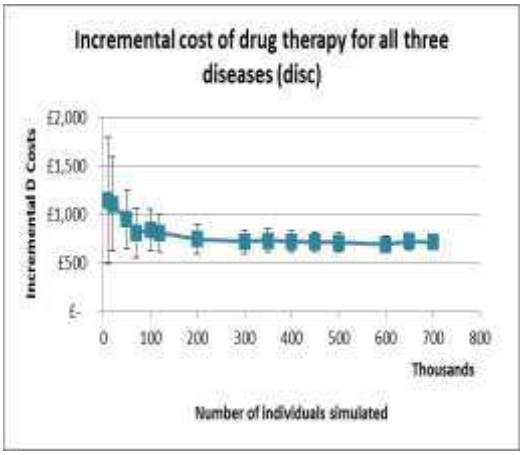
Figure S5.1. First order uncertainty in relation to the number of patients simulated in the all-disease linked model with correlations (base-year population aged 45 years and over)

1) Incremental cost (compared with none of the three treatments)

Undiscounted

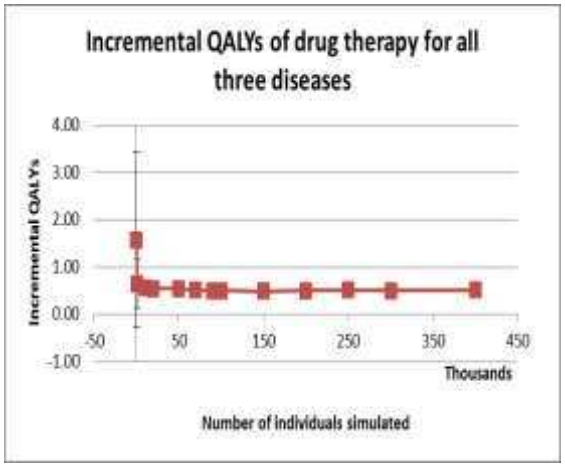


Discounted



2) Incremental QALYs (compared with none of the treatments for the three diseases)

Undiscounted



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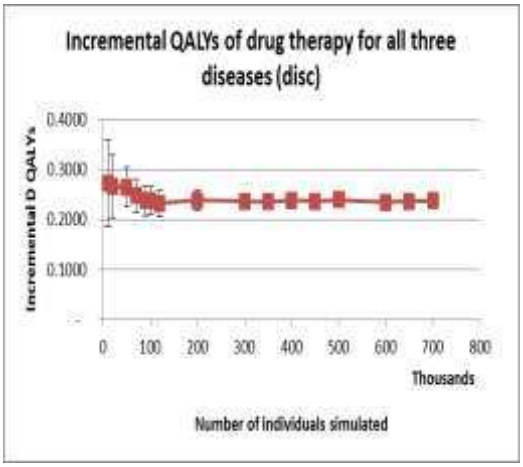
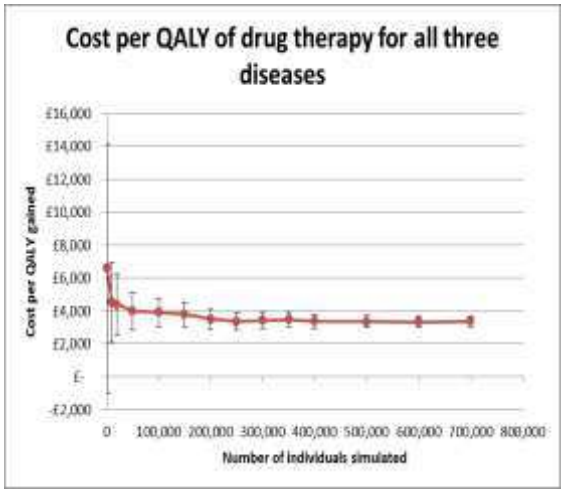
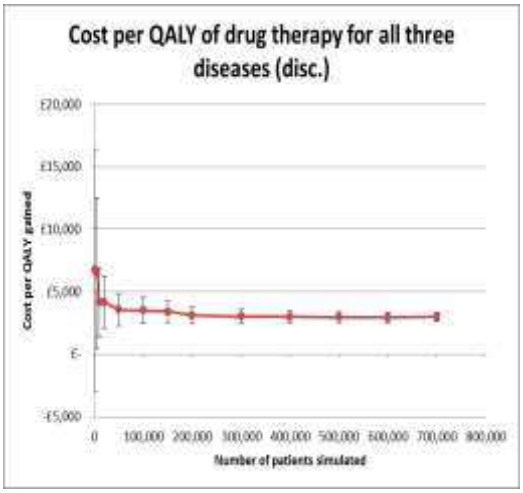


3) Cost per QALYs (95% jackknife confidence interval)

Undiscounted

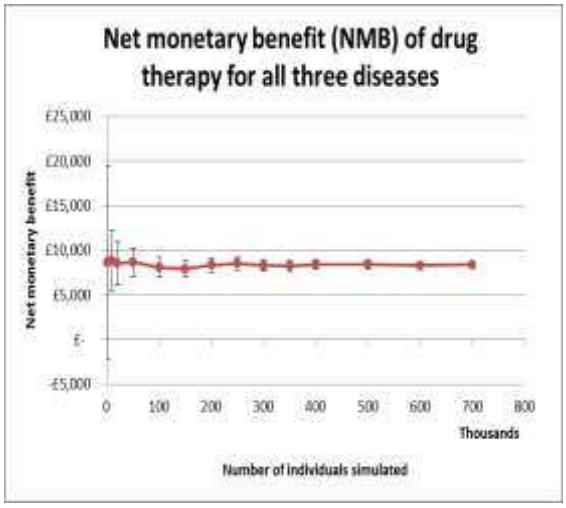


Discounted

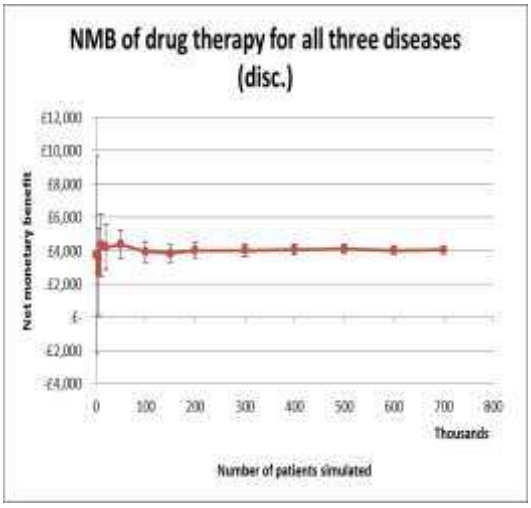


4) Net monetary benefit (£20,000 threshold)

Undiscounted



Discounted



Each figure includes error bars showing the standard error in the mean estimates of (incremental) cost and QALYs.

Appendix 6. Summary of the results from the individual disease models for comparison

	1) Heart disease only model			2) Alzheimer's disease only model			3) Osteoporosis only model			4) Sum of incremental values across 1)-3)
	Treatment	No treatment	Incremental values (A)	Treatment	No treatment	Incremental values (B)	Treatment	No treatment	Incremental values (C)	(A)+(B)+(C)
Cost - Discounted	£ 8,091	£ 7,569	£ 522	£4,582	£4,596	-£ 14	£ 2,847	£ 2,947	-£ 100	£ 408
QALYs - Discounted	9.249	8.978	0.271	10.642	10.641	0.001	11.191	11.184	0.008	0.280
Cost	£ 14,224	£ 13,197	£ 1,027	£8,845	£8,869	-£ 23	£ 6,151	£ 6,324	-£ 173	£ 831
QALYs	13.843	13.257	0.586	16.548	16.545	0.003	17.759	17.751	0.009	0.597
Life years lived	21.319	20.319	1.000	21.653	21.650	0.003	23.530	23.525	0.004	1.007
ICER – Discounted			£ 1,926 /QALY			Dominating			Dominating	£ 1,458 /QALY
ICER			£ 1,754 / QALY			Dominating			Dominating	£ 1,391 / QALY

HD: based on n=200,000; AD n=200,000; Osteoporosis n=400,000

Appendix 7. Hypothetical scenario with similar levels of QALY gains assumed for all three interventions

In order to examine the effect of sampling error when all three treatments have a similar level of QALY gains, the scenarios in Table S7.1 were assumed: these are not meant to provide accurate evaluations of current treatments but to show that the results would have face validity when QALY gains are comparable. For all three individual diseases, populations aged 65 years and older were simulated. Scenarios for larger QALY gains for AD and osteoporosis and reduced QALY gain for HD were explored. Table S7.1 shows the scenario assumptions applied to each of the three disease models in comparison with the base-case assumptions.

Table S7.1. Comparison of scenario assumptions and base-case assumptions

Base-case assumptions	Scenario assumptions
1. Heart disease model	
Relative risks were assumed to be 0.656, 0.754, 0.876, 0.59, 0.74, and 0.656 for MI, non-fatal stroke, fatal stroke, stable angina, fatal CHD, and non-cardiac death, respectively.	Relative risks of 0.98 for statin treatment were assumed for all events.
Utility values for MI, stroke and revascularisation were set to 0.76, 0.629, and 0.78, respectively.	Utility values for MI, stroke, and revascularisation were reduced to 0.5.
2. Alzheimer's disease model	
4% of monthly treatment discontinuation rate was assumed.	Lifetime treatment: No treatment discontinuation was assumed
6 months duration of treatment effect was assumed.	Lifetime treatment effect was assumed.
Utility value for institutionalised individuals was 0.33.	Utility value for those institutionalised was reduced to 0.1
The average annual improvements in MMSE score were 2.48 for donepezil and 1.4 for memantine per year.	Double treatment effect on MMSE score: the average improvements in MMSE score were set to 4.96 for donepezil and 2.8 for memantine per year.
Some individuals are institutionalised at model entry, and some patients are institutionalised immediately after diagnosis.	No individuals start at the institutionalisation state at model entry, nor get institutionalised immediately after the diagnosis (i.e. No individuals move to the

	institutionalisation event from the diagnosis event with zero time passed.)
3. Osteoporosis model	
Relative risks of fracture for alendronate treatment were set to 0.72, 0.58, and 0.82 for hip, vertebral, and other fractures, respectively.	Relative risks were assumed to be 0.33 for all fracture types.
5 years of treatment duration was assumed.	Lifetime treatment duration was assumed.

Table S7.2 compares incremental outcomes from the three individual disease models with those for each of the individual treatments from the linked model where the diseases were assumed to be independent. Under the hypothetical scenarios, a comparable magnitude of QALY gains across all three individual disease models (Table S7.2 Column a) was achieved. The margins of error around incremental costs and QALYs at 95% confidence level are shown in brackets.

Table S7.2 reports results under the scenarios in Table S7.1, assuming the diseases were independent. When none of the treatments have much larger impact on QALYs gained the linked model produced similar results to those from the individual disease models. This shows the robustness of the adoption decision within the linked model for individual treatments.

Table S7.2. Cost-effectiveness results under larger QALY gain scenarios for individual treatments from the individual disease models and the independently linked model

1. Heart disease				
	a. Individual heart disease model†	**b. Independently linked model (n=700,000)**		
	Incremental values (Margin of error) ‡	All treatments	No HD treatment*	Incremental values
DCost	£ 683 (£ 66)	£ 11,001	£ 10,201	£ 800
DQALYs	**0.0539 (0.0179)**	4.9232	4.8784	0.0448
TCost	£ 913 (£ 94)	£ 15,499	£ 14,380	£ 1,119
TQALYs	0.0875 (0.0267)	6.2589	6.1861	0.0728
ICER (disc.)	£ 12,665			£ 17,878
ICER	£ 10,433			£ 15,360
2. Alzheimer's disease (AD)				
	a. Individual AD model†	**b. Independently linked model (n=700,000)**		
	Incremental values (Margin of error) ‡	All treatments	No AD treatment*	Incremental values
DCost	-£ 4,551 (£ 93)	£ 11,001	£ 15,413	-£ 4,412
DQALYs	**0.0508 (0.0020)**	4.9232	4.8855	0.0377
TCost	-£ 6,319 (£ 130)	£ 15,499	£ 21,582	-£ 6,083
TQALYs	0.0688 (0.0028)	6.2589	6.2089	0.0500
ICER (disc.)	Dominating			Dominating
ICER	Dominating			Dominating
3. Osteoporosis				
	a. Individual osteoporosis model†	**b. Independently linked model (n=700,000)**		
	Incremental values (Margin of error) ‡	All treatments	No osteoporosis treatment*	Incremental values
DCost	-£ 1,186 (£ 74)	£ 11,001	£ 11,983	-£ 982
DQALYs	**0.0545 (0.0128)**	4.9232	4.8918	0.0314
TCost	-£ 1,856 (£ 123)	£ 15,499	£ 16,970	-£ 1,471
TQALYs	0.0900 (0.0204)	6.2589	6.2090	0.0499
ICER (disc.)	Dominating			Dominating
ICER	Dominating			Dominating

† Based on n=200,000 for HD and AD models; and n=400,000 for osteoporosis model, as in the base-case; **‡** Margin of error at 95% confidence level; *****The other two default treatments were assumed to be available; D=discounted.

When all the individual disease models produce similar QALY gains (without any disease with a significantly larger impact) the impact of Monte Carlo error for one disease on the incremental outcomes and cost-effectiveness of the other diseases can be much less influential. None of the margin of error estimates in Table S7.2 (0.0179, 0.0020, and 0.0128 for HD, AD, and osteoporosis models, respectively) will have a significant effect that changes the +/- signs of the values on the incremental QALY results from the linked model (0.0448, 0.0377, and 0.0314 for HD, AD, and osteoporosis treatments, respectively). Hence, when QALY gains are similar across all diseases, the results are less susceptible to sampling error from the other diseases. The base-case estimated very small QALY gains for AD and osteoporosis treatments which could fluctuate between positive and non-positive values due to the sampling error associated with the treatment for HD. In cases where QALY gains are similar, however, the proposed methods of linking individual disease models are likely to produce more accurate cost-effectiveness estimates for individual treatments.

Appendix 8. Probabilistic sensitivity analysis of the correlated linked model results

The correlated linked model for the three diseases (HD, AD and osteoporosis) was built probabilistically to take account of the uncertainty around input parameter point estimates. This section provides probabilistic results in order to show the feasibility of probabilistic sensitivity analysis (PSA) using the linked model described in this paper.

A probability distribution was defined for selected input parameters. The selection of parametric distributions was based on the nature of the data. For example, utilities were assumed beta-distributed as the data were assumed to be bounded by zero and one. Wherever possible, probabilistic distributions reported in the original publications of the reference models [13, 17, 18] were used. Where this was not possible, the distribution was parameterised using estimates of the error around mean or assumed standard errors for the purpose of this feasibility run of PSA. Table S8.1 shows the PSA input parameters and their distributional properties.

Table S8.1. Variables and distributions used in the probabilistic sensitivity analysis (PSA)

PSA Variable	Point estimate*	Distribution	Distributional properties
Clinical effectiveness			
RR of statin treatment for MI	0.656	Lognormal	Lognormal(logmean=-0.4219, logSE=0.0233)
RR of statin treatment for stroke	0.754	Lognormal	Lognormal(logmean=-0.2826, logSE=0.0203)
Change in MMSE when using Donepezil 10mg	1.24**	Normal	Normal(1.24, 0.22)
Change in MMSE when using Memantine 20mg	0.70**	Normal	Normal(0.70, 0.35)
Proportion of patients compliant to medication	0.75	Beta	Beta(13.31, 4.44)
Utilities of health states			
Stable angina	0.808	Beta	Beta(86.00, 20.44)
Unstable angina	0.77	Beta	Beta(93.67, 27.98)
MI	0.76	Beta	Beta(427.09, 134.87)
Stroke	0.628	Beta	Beta(91.07, 53.94)
MMSE: 0-9	0.33	Beta	Beta(36.59, 74.28)
MMSE: 10-14	0.49	Beta	Beta(78.04, 81.22)
MMSE: 15-20	0.5	Beta	Beta(856.27, 856.27)
MMSE: 21-25	0.64	Beta	Beta(1137.19, 639.67)
MMSE: 26-30	0.69	Beta	Beta(282.51, 126.92)
Institutionalised	0.33	Beta	Assumed the same as the utility

			value for MMSE:0-9
Vertebral fracture – 1st year	0.626	Beta	Beta(14.03, 8.38)
Vertebral fracture – subsequent year	0.909	Beta	Beta(6.61, 0.66)
Hip fracture – 1st year	0.792	Beta	Beta(12.26, 3.22)
Hip fracture – subsequent year	0.813	Beta	Beta(11.55, 2.66)
Costs			
Cost of institutionalisation	£2941	Normal	Normal(2941, 108)
Cost of death from hip fracture	£9525.86	Gamma	Gamma(scale=67.19, shape=141.78)***

MMSE: mini mental score examination; *mean values used in base-case analysis; **6month estimate; ***calculated from assumed standard error of 800.

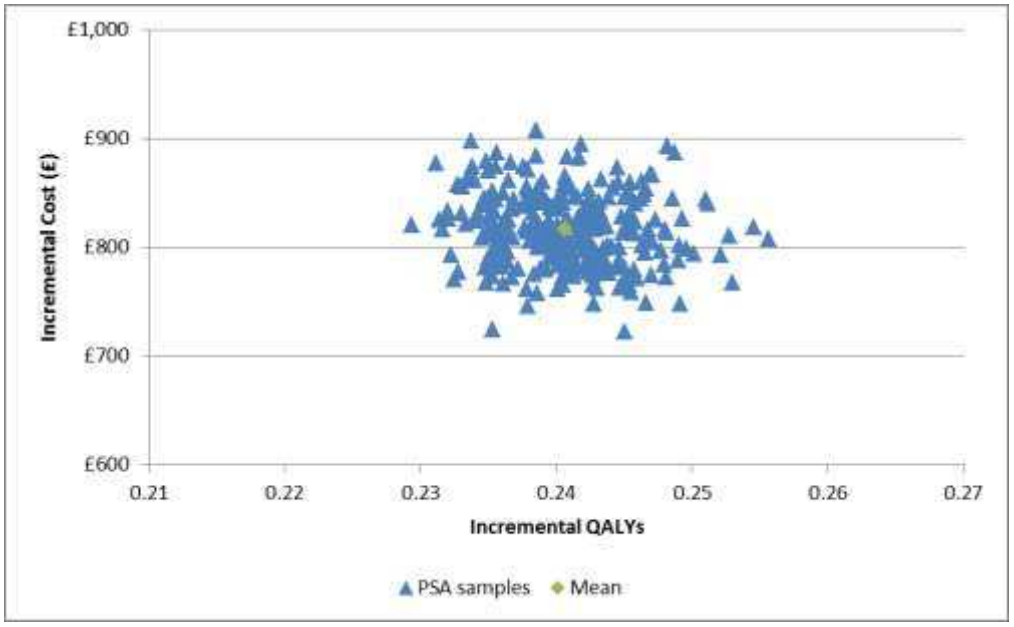
The probabilistic model results are shown in Table S8.2 based on 300 PSA runs in each of which 700,000 individuals were simulated. The mean cost and QALYs of the PSA results in Table S8.2 showed comparable results with the base-deterministic results from the correlated linked model albeit not identical. All of the PSA samples in Figure S8.1 showed cost per QALY being lower than the threshold of £20,000 per QALY gained.

Table S8.2. Comparison of probabilistic model results with the base-case deterministic results*

All-disease linked model with correlations	Deterministic results			Probabilistic results		
	All three treatments assumed	None of the three treatments assumed	Incremental values	All three treatments assumed	None of the three treatments assumed	Incremental values
Mean cost	£14,741	£13,894	£847	£14,392	£13,575	£816
Mean QALYs	8.962	8.725	0.236	8.972	8.731	0.241
ICER			£3,583/QALY			£3,391/QALY**

*Based on 300 PSA runs; each deterministic run is based on 700,000 simulated individuals;
**Jackknife 95% C.I. £3,360-£3,423.

Figure S8.1. Probabilistic sensitivity analysis scatterplot of incremental costs and QALYs



*Based on 300 PSA runs

The results show that the adoption decision is robust when assuming the willingness-to-pay threshold of £20,000 per QALY gained. Each deterministic run of 700,000 individuals took approximately 15 minutes to run and hence, conducting 300 PSA runs for each intervention arm took 1.9 days of computing time (Intel Core™ i7CPU 3.40GHz processor with 16GB RAM). Such time scales indicate it is feasible to conduct PSA using the multi-disease linked model. The probabilistic analysis of discrete event simulation model will become more achievable by using a computer with more processing power or parallel computing. The number of runs required would be affected by the homogeneity of the population studied. Hence, the use of a more narrowly defined population with specific characteristics and higher disease prevalence, than the general population adopted in the current analysis, would accelerate convergence due to higher number of disease events simulated and more homogeneous parameter values.

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