Institute and Faculty of Actuaries

Developing disease-based models

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15 September 2014

Agenda

1. **Objectives**
2. **Overview**
3. **Data**
   - Datasets
   - Research papers
   - Expert judgement
4. **Model structure**
   - Multistate model
   - Disease groupings
   - Comorbidities
5. **Case studies**
6. **Demonstration**

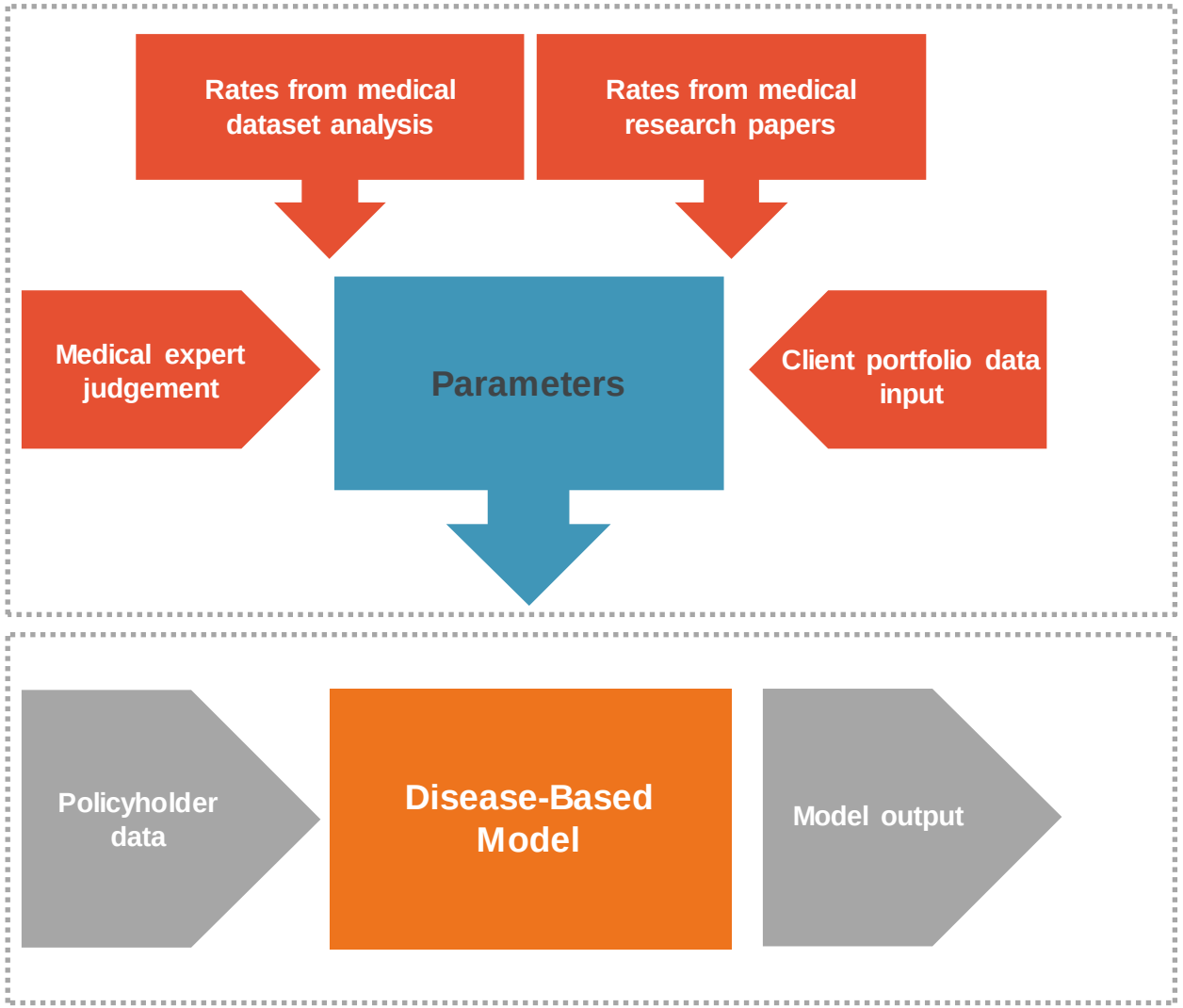
Objectives

Objectives

- What are the objectives of a Disease-Based Model?
- Improved modelling where medical states or events are critical (eg enhanced annuities)
- A better view of improvements (best estimate) via appropriate ‘per disease’ expert judgement
- A better view of biologically plausible improvement stresses
- A bottom-up ‘future-oriented’ projection method compared with typical traditional approach to mortality modelling
- Disease-based rather than cause of death

Overview

Overview


Rates from medical dataset analysis
Rates from medical research papers
Medical expert judgement
Parameters
Client portfolio data input
Policyholder data
Disease-Based Model
Model output

Data

Data

- There are three broad sources of data used for model development
  - Rich datasets
  - Research papers
  - Expert judgement
- There is also the important question of what data we receive from potential policyholders for underwriting purposes, and how accurate it is

Datasets

- Medical datasets
  - ***CPRD***
  - ***Framingham***
  - THIN
  - QResearch
  - EUROCARE
  - ***SEER***
  - HES
  - ONS
  - Many others …

- Primary criteria are:
  - Availability of data
  - Relevance of data (basis risk?)
  - Reliability
  - Granularity
  - Risk factor information

CPRD

- Circa 6 million UK GP/patient records
- Observational data and interventional research service funded by NHS
- Information recorded at anonymised person-level although information accessed at aggregate level only
- Data includes prescribed primary care and hospital administered drugs, disease and cancer registers, and GP notes
- SES data available through linkages to census data by postcode
- Licensed by various insurers and reinsurers

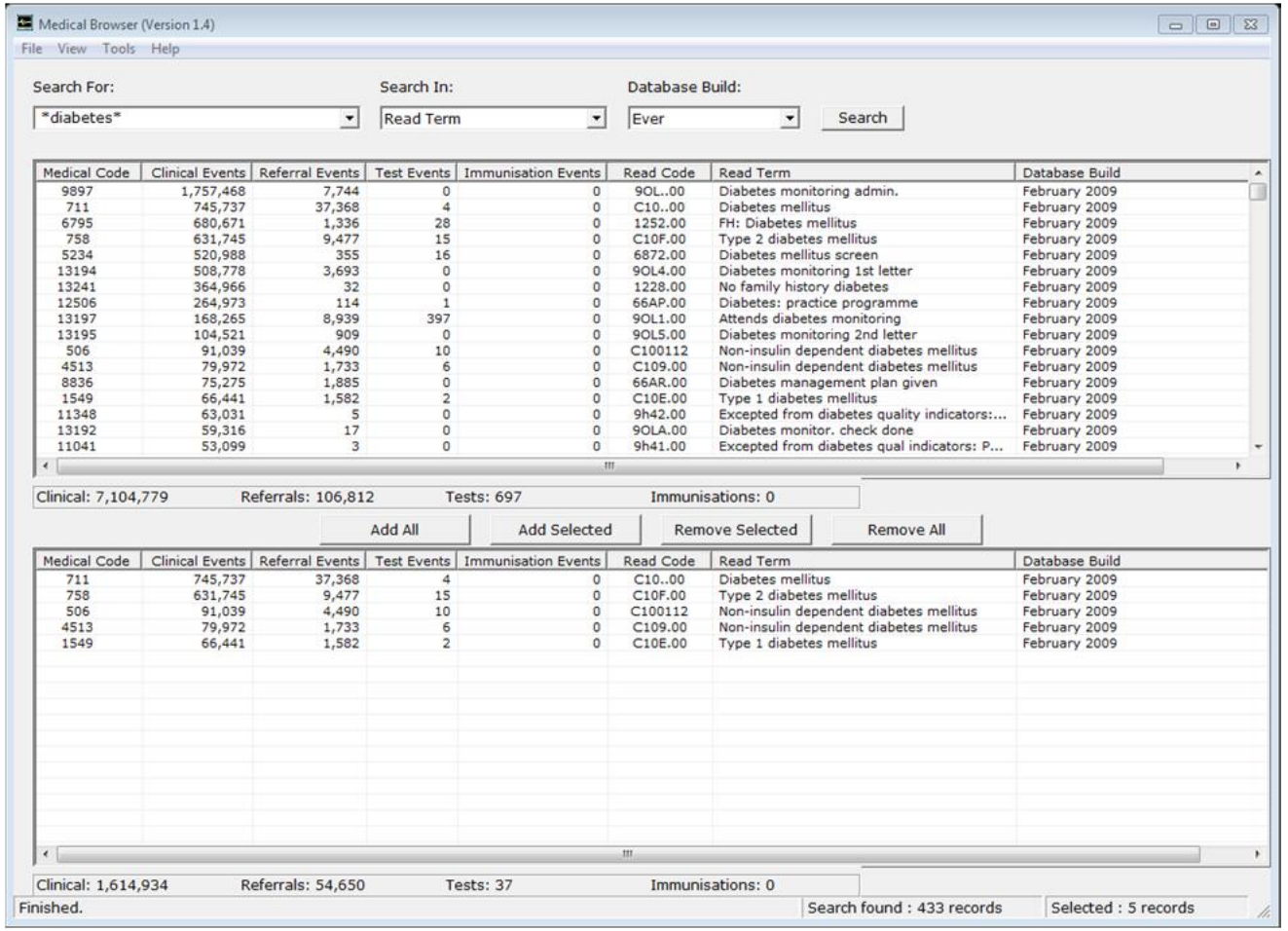
Extracts can be defined with the following factors:

- Age
- Gender
- Duration
- Smoker status
- SES quintiles
- Calendar year

Severity can be accessed via clinical test results, including:

- HbA1c for diabetics
- Systolic BP
- Serum cholesterol levels
- BMI
- HDL, LDL and ratio
- ALT levels (liver function)

CPRD – defining Pegasus codes to access the data



All entries containing the term “diabetes”

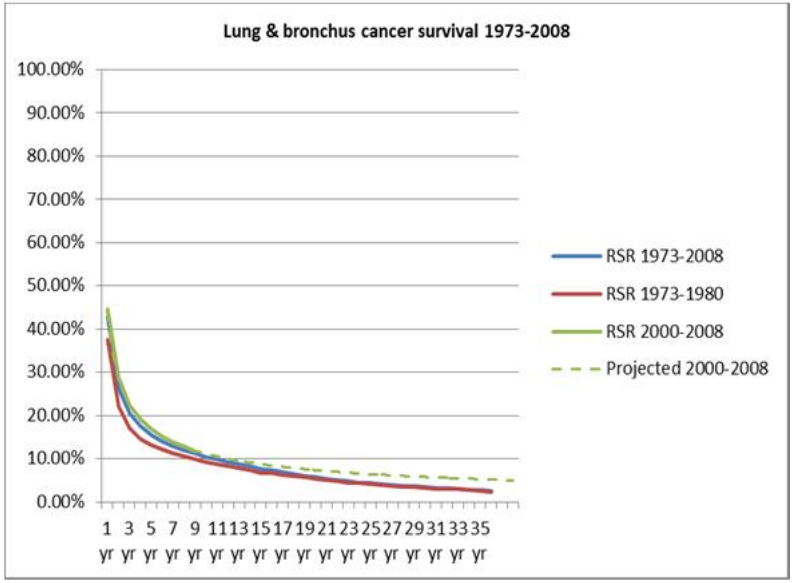
Selecting relevant codes to form a diabetes disease group.

Framingham

- Framingham heart study is a long-term US research project
- Since initiation in 1948, three generations have joined totalling participation of over 9,000 individuals
- The core research of the heart study has focused on cardiovascular and cerebrovascular disease and related risk factors
- Contains individual level data recorded biennially
- Framingham phenotypic data is stored in SAS datasets, each dataset is accompanied by a coding manual (containing definitions)
- NIH has launched Framingham SHARe – summary data now available online, request for access needed for patient specific

SEER / JR Dataset

- Surveillance Epidemiology & End Results
- Large US cancer database with cases going back to the 1970s
- Currently covering about ¼ US population
- Freely Available
- Most forms of cancer analysable using individualised data
- UK Cancer registry data not freely available


Lung & bronchus cancer survival 1973-2008
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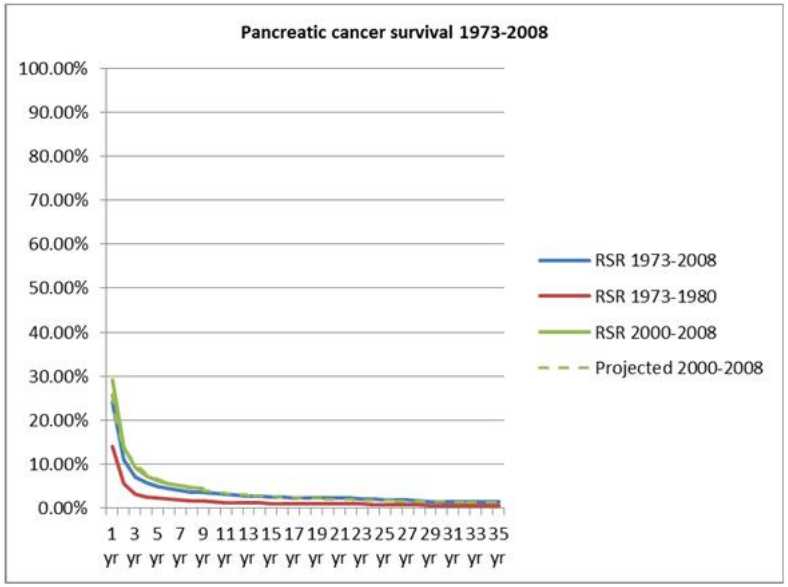
RSR 1973-2008
RSR 1973-1980
RSR 2000-2008
Projected 2000-2008


Pancreatic cancer survival 1973-2008
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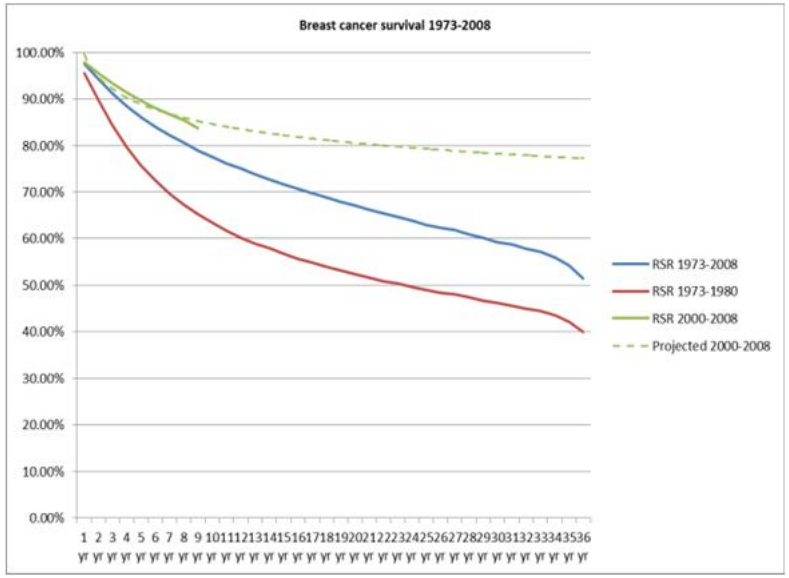
RSR 1973-1980
RSR 2000-2008
Projected 2000-2008


Breast cancer survival 1973-2008
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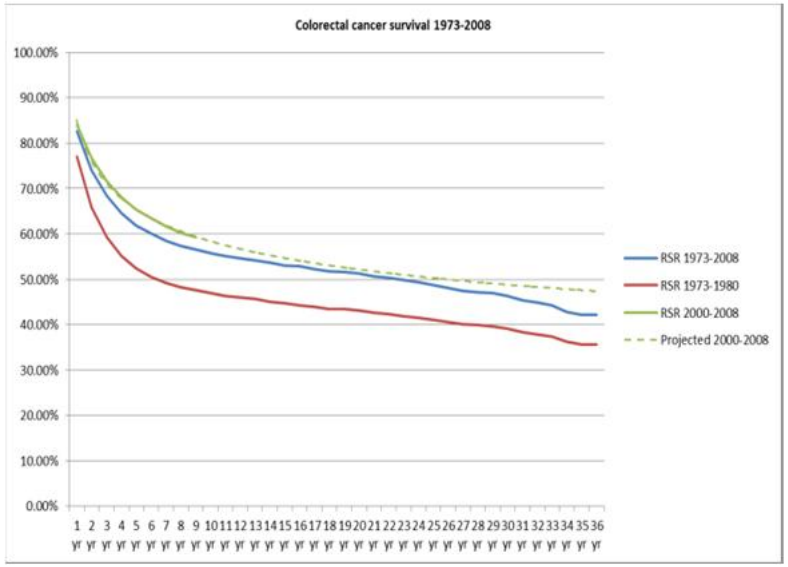
RSR 1973-2008
RSR 1973-1980
RSR 2000-2008
Projected 2000-2008


Colorectal cancer survival 1973-2008
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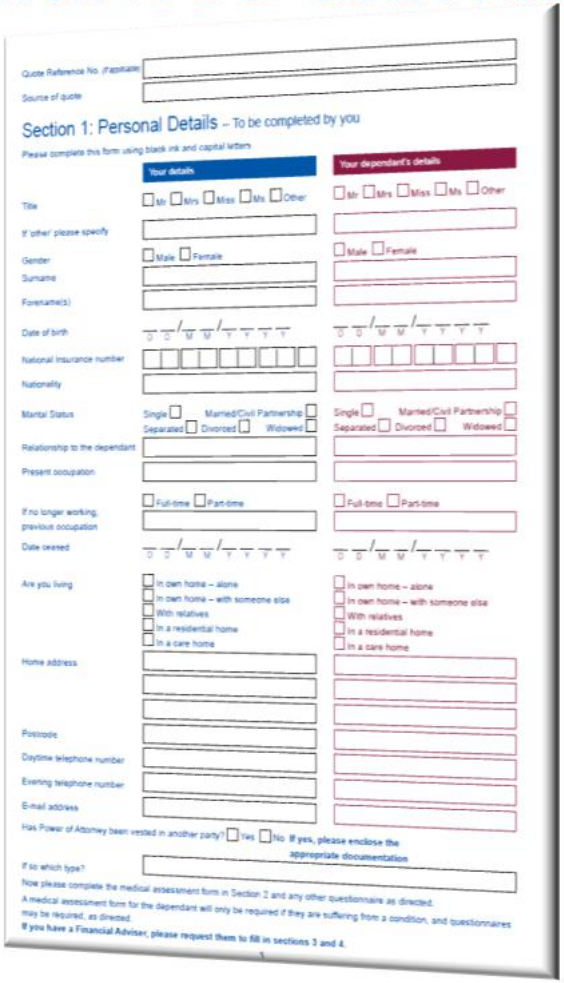
RSR 1973-2008
RSR 1973-1980
RSR 2000-2008
Projected 2000-2008

As good as the questions you ask

- Underwriting systems are constrained by the consensus required to acquire data from prospective customers
- Questionnaires evolve over time
- Lack of consistency
- Lack of validation

CQF: Common Quotation Form for enhanced annuities



Quote Reference No. (if applicable)

Source of quote

Section 1: Personal Details – To be completed by you

Please complete this form using black ink and capital letters

	Your details	Your dependant's details
Title	☐ Mr ☐ Mrs ☐ Miss ☐ Ms ☐ Other	☐ Mr ☐ Mrs ☐ Miss ☐ Ms ☐ Other
If 'other' please specify		
Gender	☐ Male ☐ Female	☐ Male ☐ Female
Surname		
Forename(s)		
Date of birth	D D / M M / Y Y Y Y	D D / M M / Y Y Y Y
National Insurance number		
Nationality		
Marital Status	Single ☐ Married/Civil Partnership ☐ Separated ☐ Divorced ☐ Widowed ☐	Single ☐ Married/Civil Partnership ☐ Separated ☐ Divorced ☐ Widowed ☐
Relationship to the dependant		
Present occupation		
If no longer working, previous occupation	☐ Full-time ☐ Part-time	☐ Full-time ☐ Part-time
Date ceased	D D / M M / Y Y Y Y	D D / M M / Y Y Y Y
Are you living	☐ In own home – alone ☐ In own home – with someone else ☐ With relatives ☐ In a residential home ☐ In a care home	☐ In own home – alone ☐ In own home – with someone else ☐ With relatives ☐ In a residential home ☐ In a care home
Home address		
Postcode		
Daytime telephone number		
Evening telephone number		
E-mail address		

Has Power of Attorney been vested in another party? ☐ Yes ☐ No **If yes, please enclose the appropriate documentation**

If so which type?

Now please complete the medical assessment form in Section 2 and any other questionnaire as directed.

A medical assessment form for the dependant will only be required if they are suffering from a condition, and questionnaires may be required, as directed.

If you have a Financial Adviser, please request them to fill in sections 3 and 4.

Infinite number of permutations

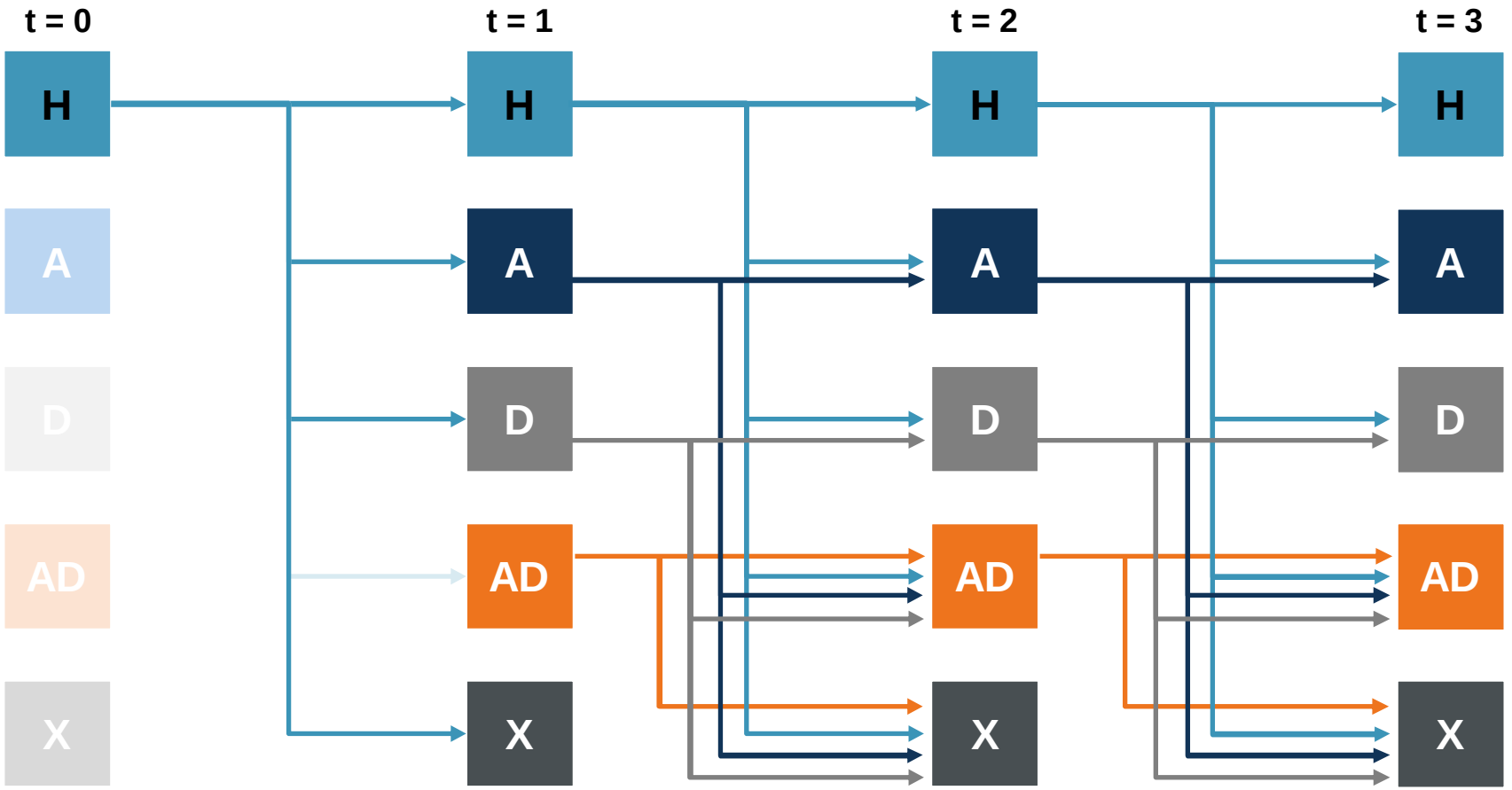
AVIVA · Canada Life · FriendsLife · justretirement · Legal & General · LV= · mgmadvantage · partnership · PRUDENTIAL

Model structure

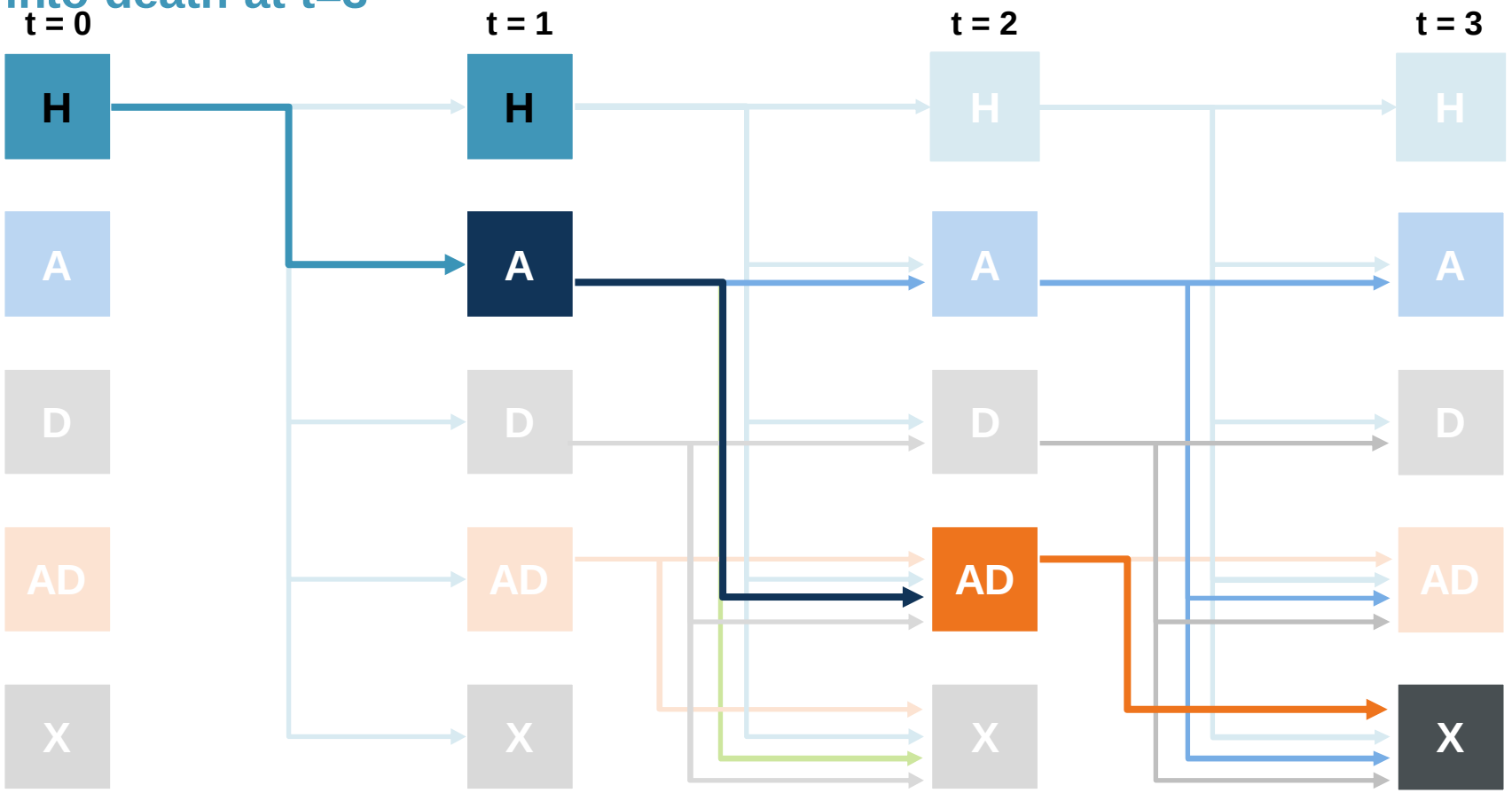
Model structure

- Overall structure
- Groupings
- Parameterisation
- Comorbidities

Multistate – simplified Angina / Diabetes / Comorbidity example



A single simulation path: policyholder transitions through A, AD into death at t=3



Diseases and groups

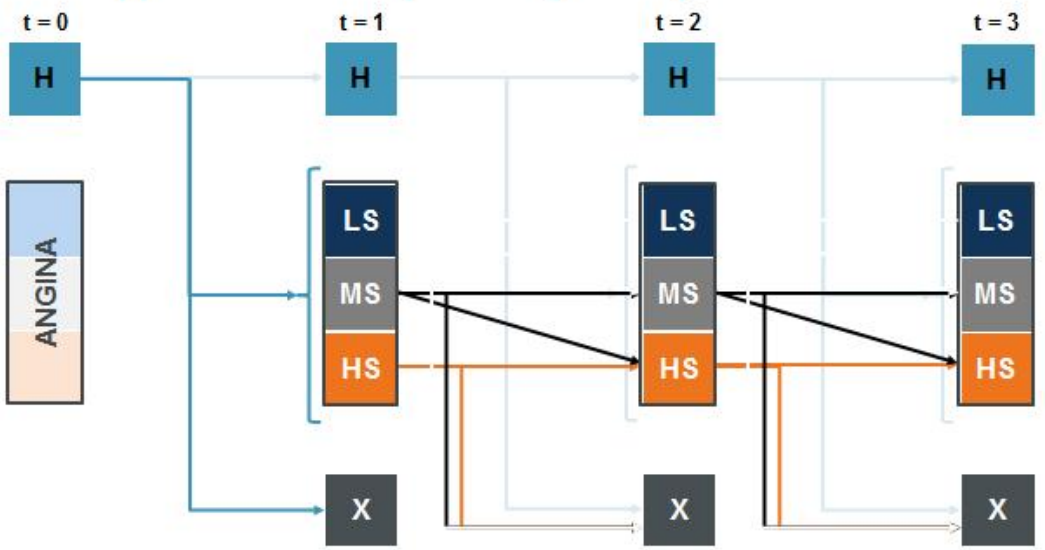
- How can diseases and disease groups differ (i.e. what defines a homogeneous disease group?):
  - The mortality/survival shape over time (both time as age, and time as duration)
  - The effect of risk factors (eg smoking effect on lung cancer incidence/mortality v different from colo-rectal equivalent)
- Expectations of future improvements on the age shape
- Availability of reliable data
- The crucial element in disease 'similarity' from a modelling perspective is the age curve. Differences in the effect of other risk factors (e.g. smoking status) can be accommodated by appropriate interactions where necessary

Disease groupings

Disease Group (from CQF)	Specific Disease
Heart attack, angina and other vascular conditions	Angina, MI, Cardiomyopathy …
Diabetes	Type I Diabetes, Type II Diabetes
Cancer, leukaemia, lymphoma, growth or tumour	Breast, Colorectal, Lung, Prostate …
Stroke	Haemorrhagic, ischaemic …
Respiratory/lung disease	COPD, Emphysema …
Multiple sclerosis	MS
Other neurological condition	Dementia, Alzheimer's disease, Parkinson's disease, Motor neurone disease …
ADLs	…

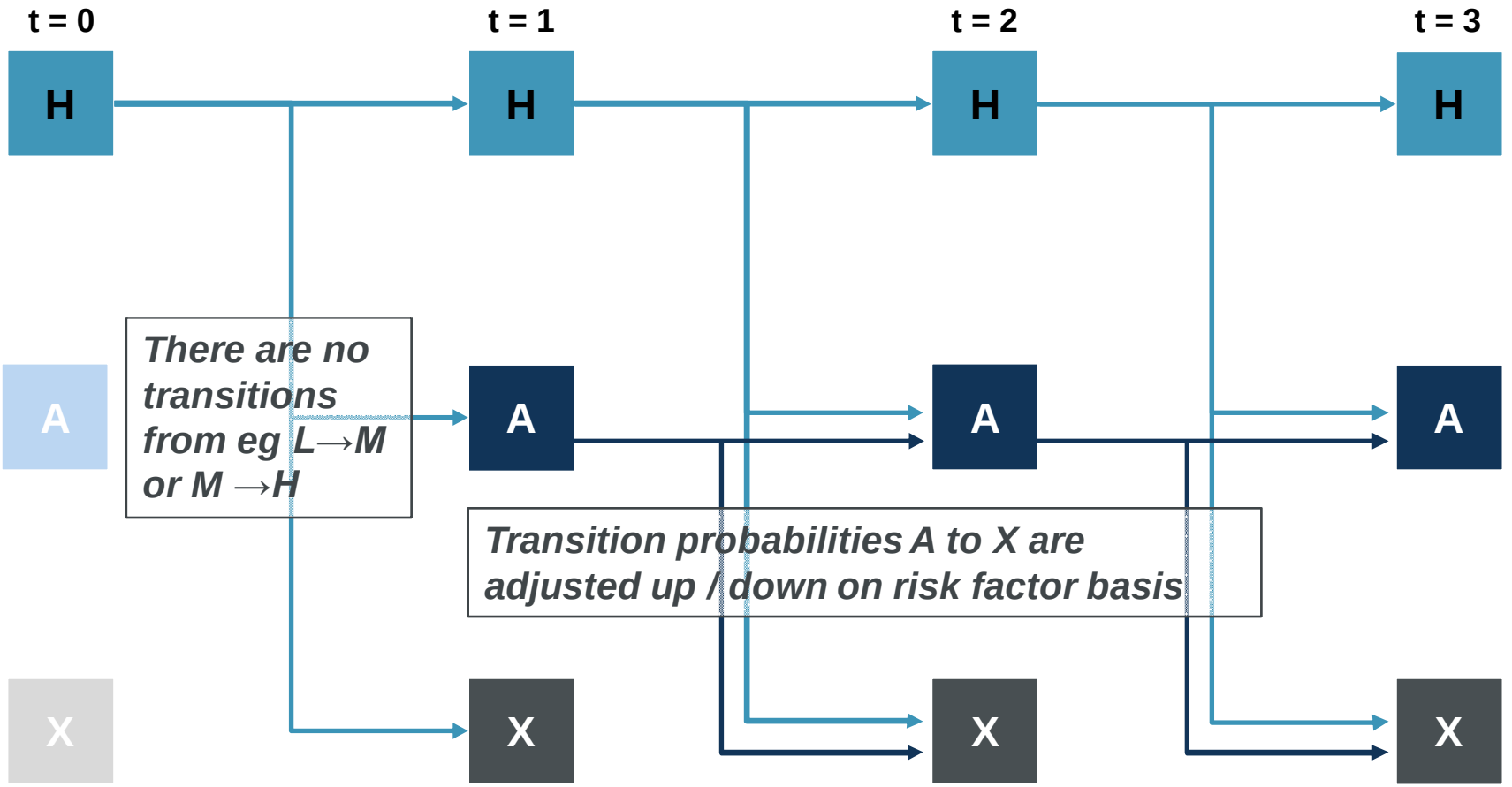
Severity Modelling

- Could model via explicit state approach – eg with three severity states (low / medium / high)



- Alternative approach is to treat severity as a risk factor (ie no explicit state)

Risk factor approach to severity modelling



Paramaterisation (from CPRD)

- Need a parameterisation approach that allows us to derive maximum value from the data in the CPRD, with particular reference to the following criteria
  - Multi-factor analysis
  - Automatic allowance for correlations in the data
  - Non-parametric approach in general (so results not forced to any particular function), but with parametric options where useful (eg age curve)
  - Efficient usage of data (ie needs to cope well where ‘pockets’ of data in respect of particular unique combinations of rating factors are sparse or even empty)
  - Easy allowance for factor interactions
  - Common usage across the insurance sector
- Accordingly we use Generalised Linear Models (GLMs) for the parameterisation

Risk factors

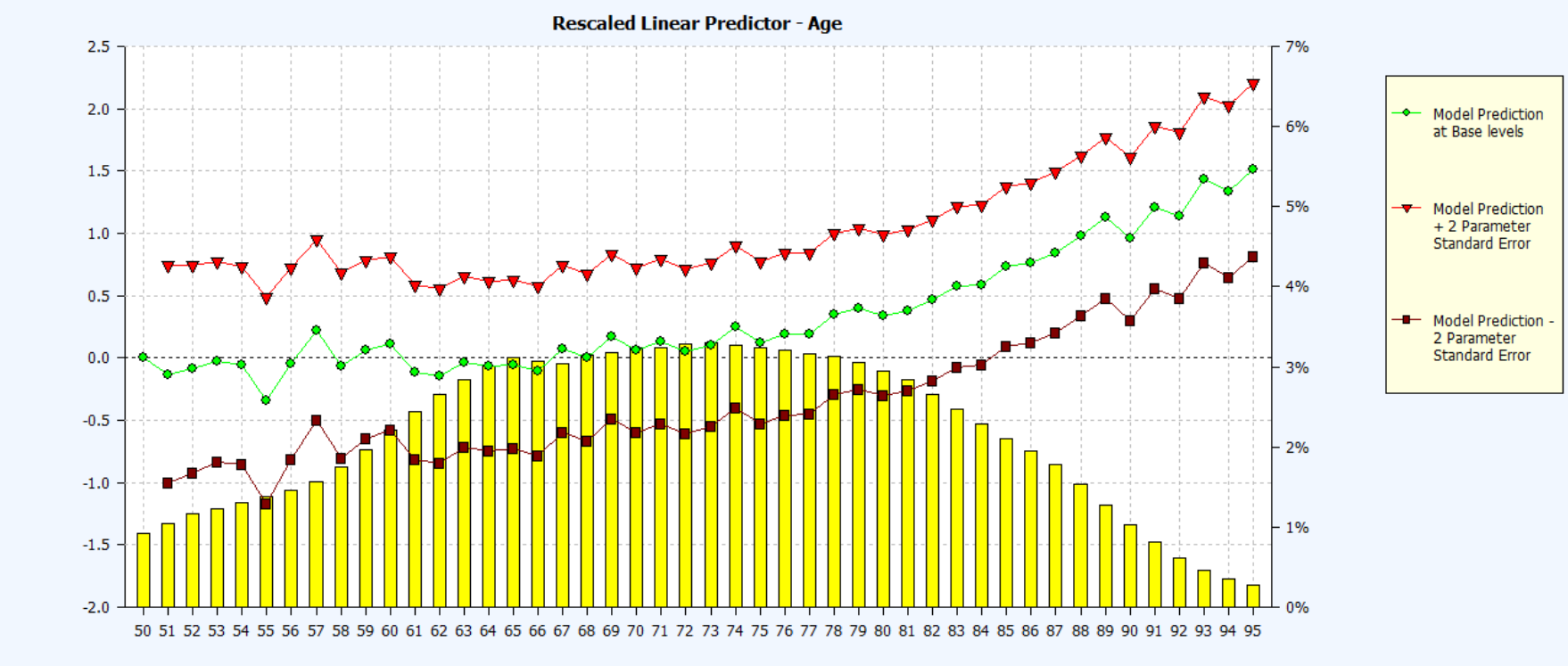
Using CPRD, the following can be used as risk factors:

- Age
- Gender
- Duration
- Smoker status
- SES quintiles
- Calendar year

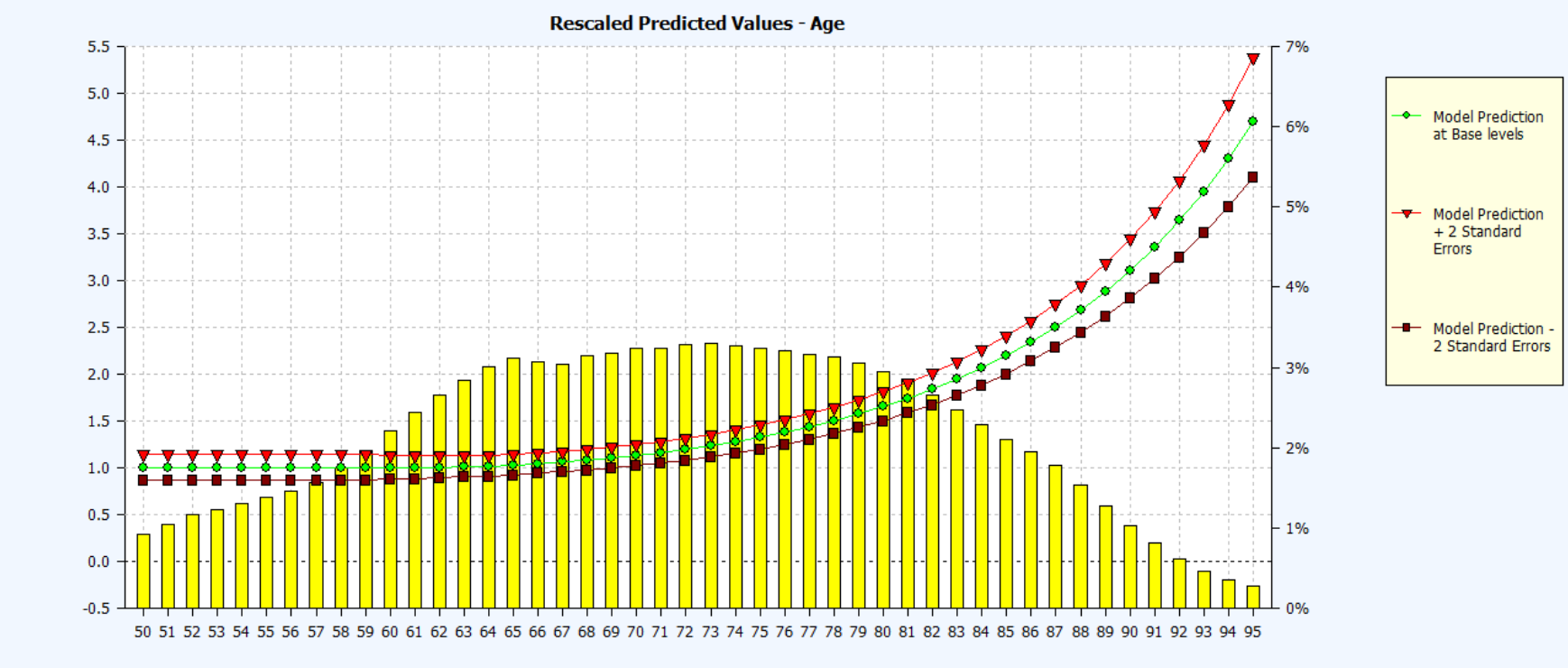
Clinical test results from CPRD to use as risk factors include:

- HbA1c for diabetics
- Systolic BP
- Serum cholesterol levels
- BMI
- HDL, LDL and ratio
- ALT levels (liver function)

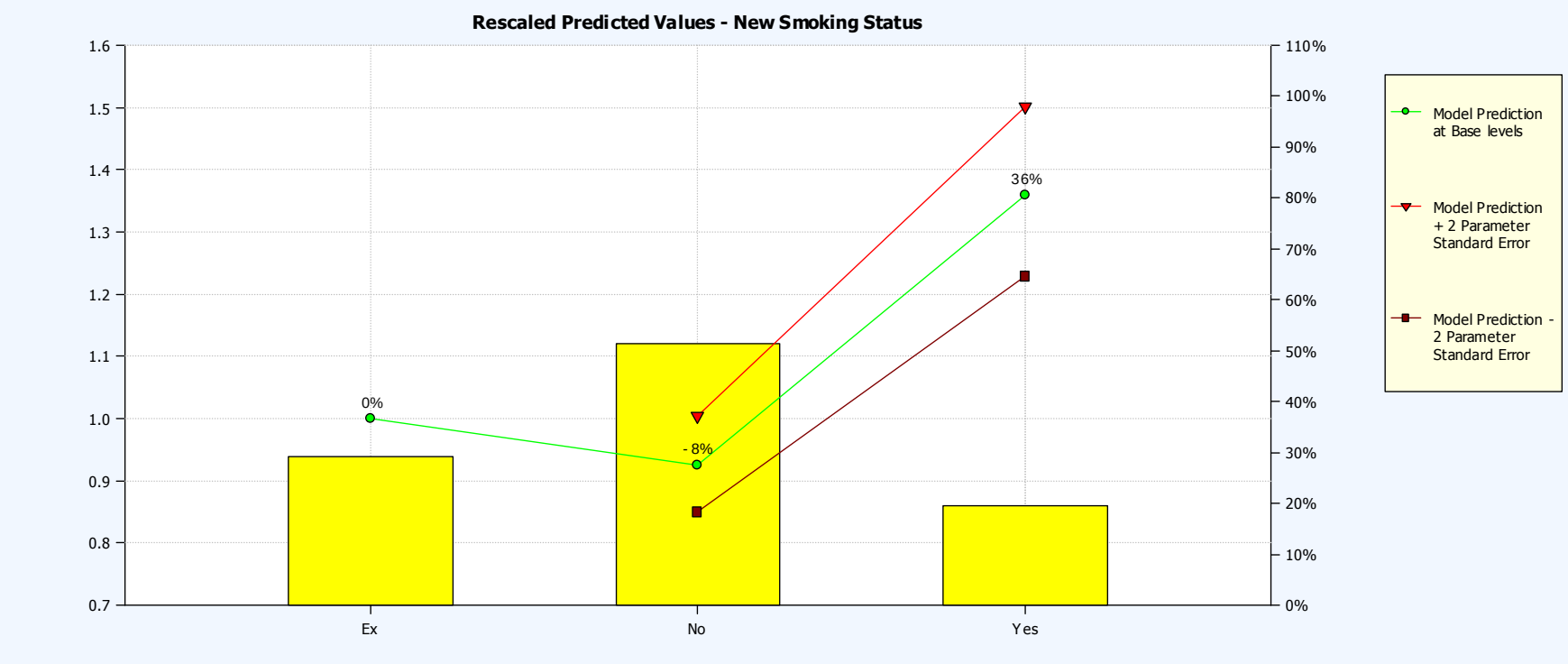
GLM of cancer mortality
Age – ‘raw’ (all cancers grouped)



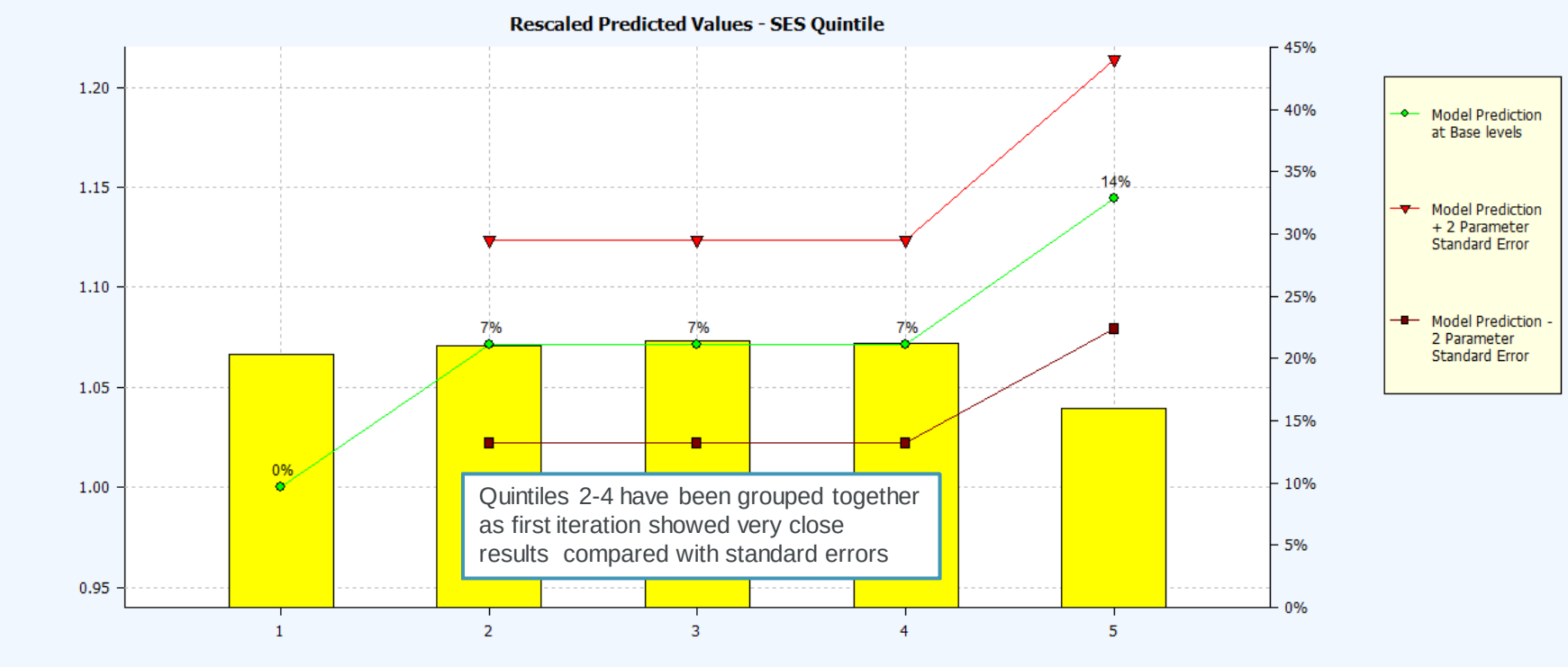
GLM of cancer mortality
Age – smoothed (all cancers grouped)



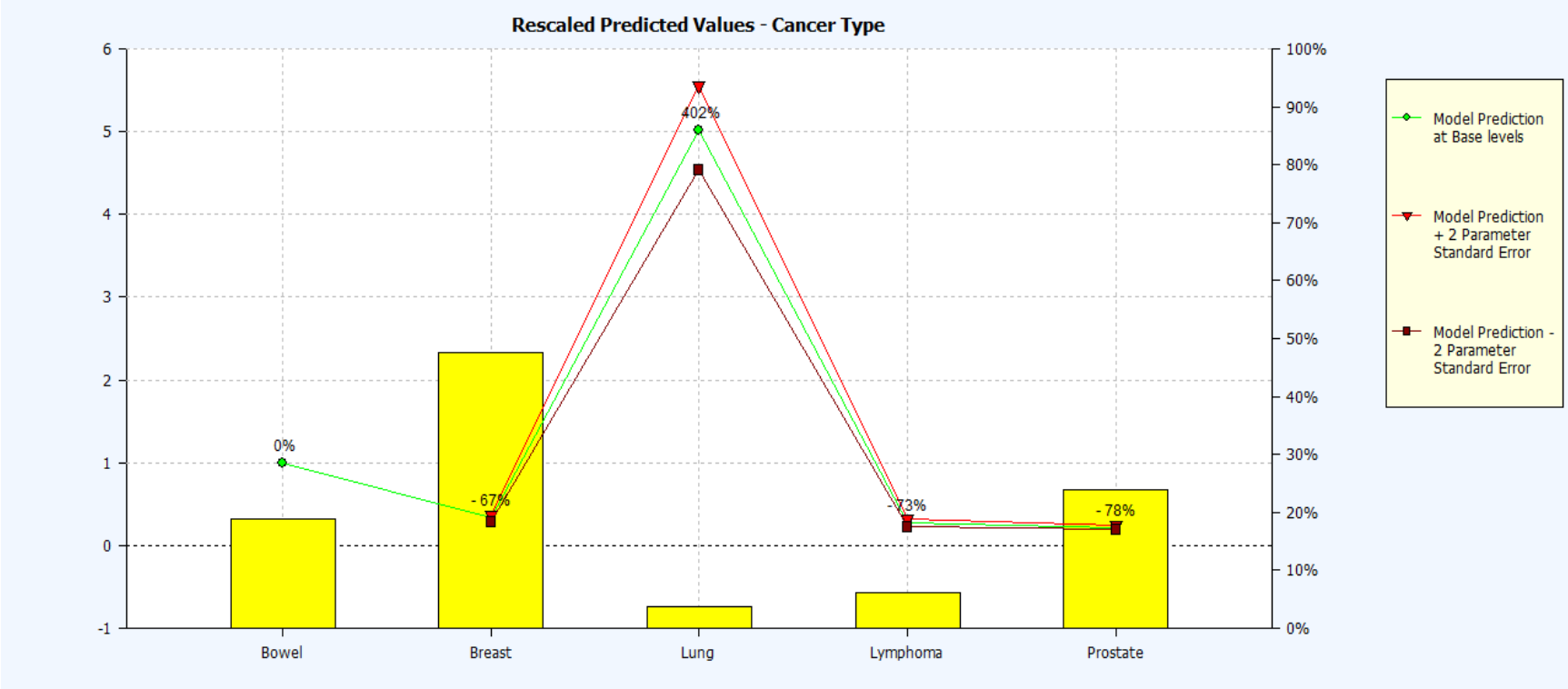
Cancer mortality – smoking status



Cancer mortality – SES quintile

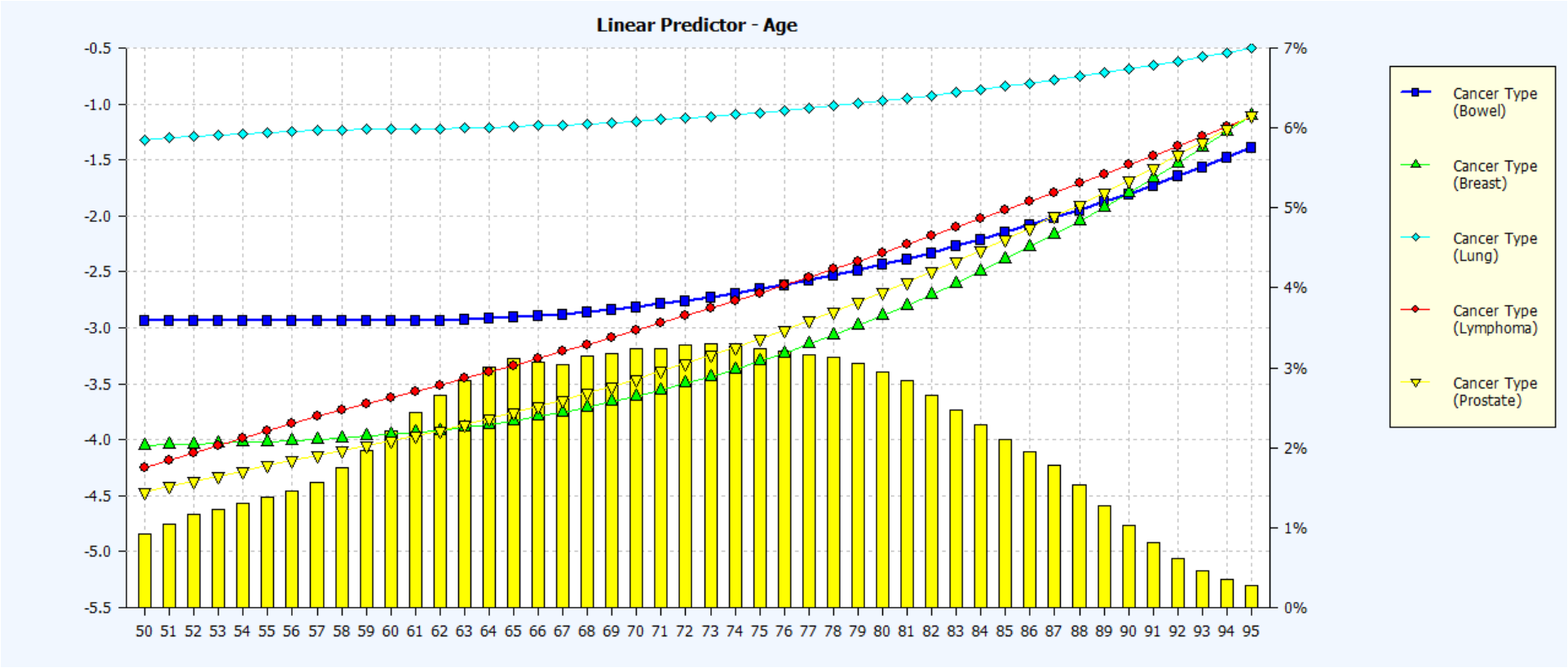


Cancer mortality – type of cancer

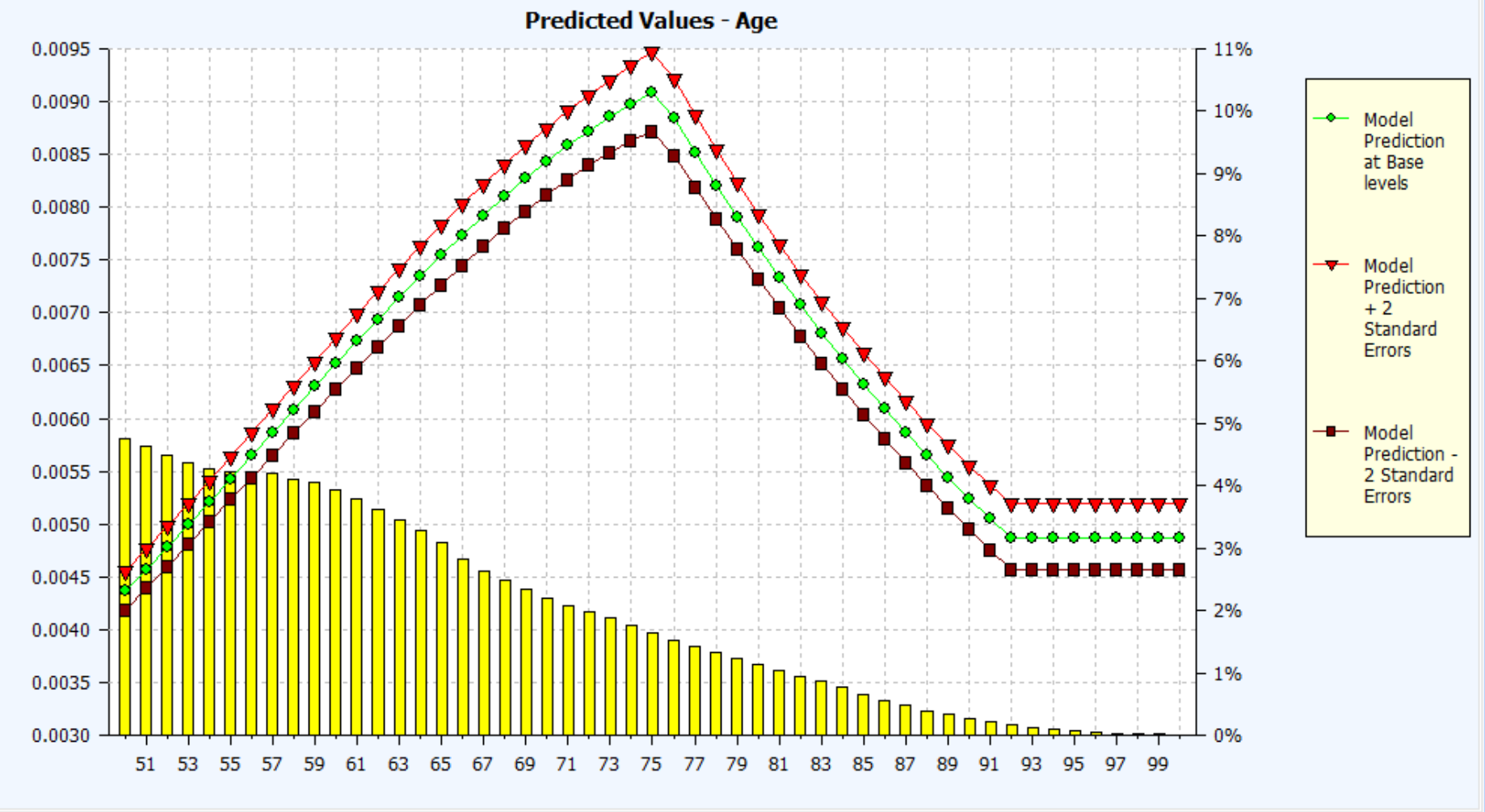


Age x Cancer Type Interaction

The model allows the age curve to vary by cancer type. This graph shows the 5 age curves together. Prostate and breast cancer have very similar shapes, while the others are all distinct.



GLM – Healthy to Diabetic – Age result



Comorbidities – significance

- Essential feature
- What comorbidities to model?
  - Material prevalence (and corresponding availability of data)
  - Mortality 'interaction' ie the two morbidities compound to make the mortality effect 'greater than the sum of the parts'
  - Extent of published research
  - Common pathogenesis
- Model complexity
  - Structure
  - Availability of data to parameterise transitions into / out of comorbidity?
  - Other routes to modelling comorbidity effect?

Comorbidity example

Diabetes and heart disease

- Diabetes promotes insulin resistance and mechanisms that alter the function and structure of blood vessels leading to a propensity for platelet aggregation and coagulation and an increased risk of plaque rupture. Thus a diagnosis of diabetes is a significant risk for cardiovascular disease.
- Framingham data analysis reveals that the incidence of CVD among diabetic men and women compared with non-diabetic individuals is x2 and x3 respectively. Mortality from CVD was also increased in diabetics with a relative risk of x1.7 and x3.3 respectively.
- Mortality hazard ratios for those with diabetes compared with those without are significantly increased in a number of causes; from 1.25 for cancer deaths to 3.03 for vascular deaths.
- This is dependent upon HbA1c levels, duration of disease, cholesterol and blood pressure levels and smoking status with a range of life expectancy at age 55 years from 13 to 21 years dependent upon these factors.

Diabetes and heart disease – references

- Clarke R et al, (2009), Life expectancy in relation to cardiovascular risk factors: 38 year follow-up of 19 000 men in the Whitehall study. *British Medical Journal*, doi:10.1136/bmj.b3513
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- Kannel W and McGee D (1979), Diabetes and Glucose Tolerance as Risk Factors for Cardiovascular Disease: The Framingham Study, *Diabetes Care*, VOL. 2 NO. 2, MARCH-APRIL 1979
- Miki Tet al (2012), Effects of diabetes on myocardial infarct size and cardio-protection by pre-conditioning and post-conditioning, *Cardiovascular Diabetology* 2012, 11:67
- Haffner S et al (1998), Mortality From Coronary Heart Disease In Subjects With Type 2 Diabetes And In Nondiabetic Subjects With And Without Prior Myocardial Infarction, *New England Journal of Medicine* 1998;339:229-34
- SIscoviek D et al (2010), Type 2 Diabetes Mellitus And The Risk Of Sudden Cardiac Arrest In The Community, *Rev Endocr Metab Disord* (2010) 11:53–59

Diabetes and cancer

- Various studies suggest that the risk for several types of cancer is increased in diabetic patients; mortality has also been found to be increased in this population. These two conditions are increasingly likely to co-exist.
- Some linkage observed between colorectal cancer and insulin resistance. Insulin resistance (and hyperinsulinaemia) may increase risk of colon cancer.
- Re possible shared pathogenesis, the process of insulin resistance serves to promote cellular proliferation and inhibit apoptosis in many tissue types possibly resulting in tumourigenesis.
- Vinikoor et al (2009) found patients with colon and rectal cancer had a higher prevalence of diabetes - odds ratio x1.4 for colon cancer for whites (borderline significance)
- Stocks T et al (2008) in their study suggested that the presence of obesity, hypertension and hyperglycaemia significantly increased the risk of colorectal cancer (eg x2.4 if two metabolic syndrome indicators)
- The combined summary odds ratio for pancreatic cancer associated with type II diabetes was x1.8 (Huxley et al, 2005).

Diabetes and cancer – references

- Swerdlow A et al (2005), Cancer incidence and mortality in patients with insulin-treated diabetes: a UK cohort study, *British Journal of Cancer* 92:2070-2075
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- Barone B et al (2008), Long-term, all-cause mortality in cancer patients with pre-existing diabetes mellitus: A systematic review and meta-analysis, JAMA 300(23):2754-2764
- Rapp K et al (2008), Weight change and cancer risk in a cohort of more than 65,000 adults in Austria, *Annals of Oncology* 19:641-648
- Major J et al (2009). Insulin-like growth factor-I and cancer mortality in older men, *Journal of Clinical Endocrinology and Metabolism* 95(3):1054-1059
- Waters K et al (2009), Association of Diabetes With Prostate Cancer Risk in the Multi-ethnic Cohort, *American Journal of Epidemiology* 2009; 169:937–945
- Vinikoor L et al (2009), The Association Between Diabetes, Insulin Use, And Colorectal Cancer Among Whites and African Americans, *Cancer Epidemiology Biomarkers and Prevention* 18(4)
- Stocks T et al (2008), Components Of The Metabolic Syndrome And Colorectal Cancer Risk; A Prospective Study, *International Journal of Obesity* 32:304-314
- Huxley R et al (2005), Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies, *British Journal of Cancer* 92:2076-2083

Case studies

Atrial Fibrillation

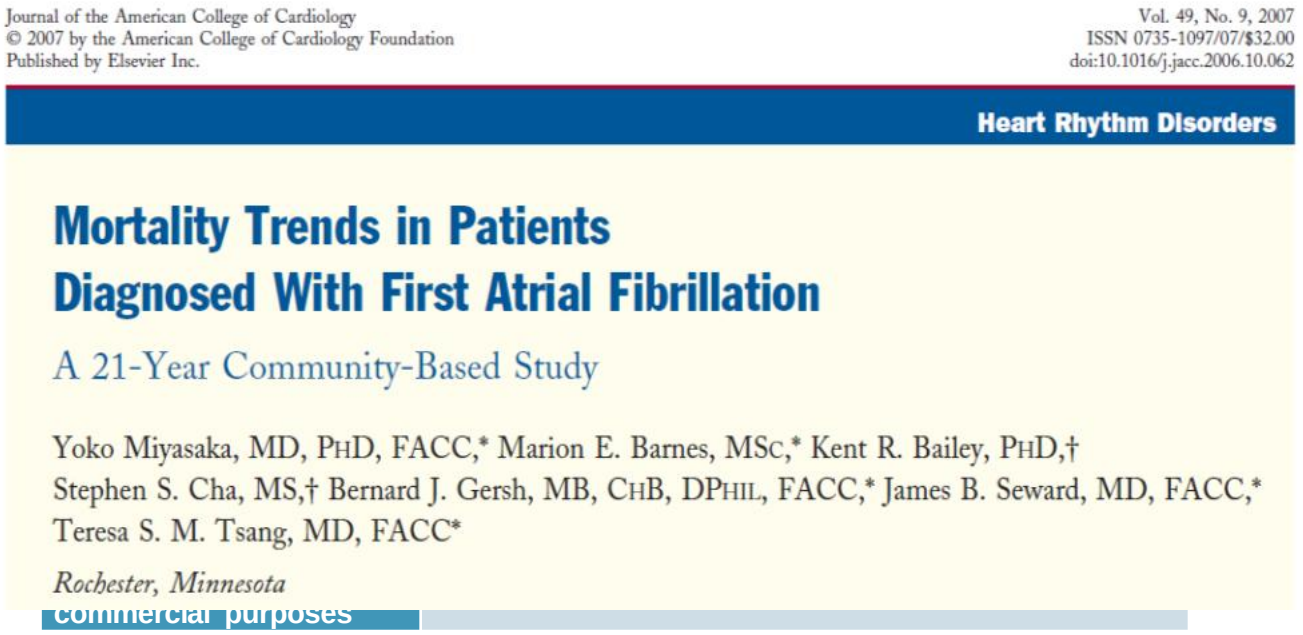
- Common condition of the elderly
  - Clots to form in the upper part of the heart
  - Risk of stroke
- Stroke is preventable with warfarin and other newer drugs
- Warfarin itself carries an additional mortality risk
- What is the size of the risk from AF?
  - How long does the risk last?
  - Is the risk the same in different people?
  - How should that risk be aggregated amongst the many other risk factors for death?

Atrial Fibrillation

- Relevant publications

First author, year	Summary	Methods	n	Country	Average (or min) age	Length of follow up	Timeframe	Outcomes	Population
Andersson, 2013	Incident AF in hospitalised patients. AF was an independent risk factor of ACM in the multivariate analysis (controlling for concomitant diseases such as HF, HBP, COPD, stroke, TIA, DM.	KM plots are used to illustrate unadjusted mortality. Cox regression mdels were used to compare AF patients with controls. A nested case-control analysis was performed to compare deceased against alive AF subjects.	272186 hospitalised patients with incidental AF	Sweden	all <85, mean age 72.3 y (+/- 10.9)	13 years max.	1995-2008 followed up until December, 2009.	All cause mortality and independent risk factors.	Data from the Swedish National Patient Registry. Hospital admissions with incident AF, 2 controls with no hospital record of AF per AF case, matched for age, gender and calendar year
Benjamin, 1998	After adjustment for age, HBP, smoking, DM, left ventricular hypertrophy, MI, CHF, HVD, stroke, TIA, AFT was associated with OR for death of 1.5	Pooled logistic regression (allowing covariates change over time in multivariate analysis). For every AF patients there were 2 subjects without AF matched by age, sex, date of diagnosis, shown in the KM analysis.	621 AF out of 5209 subjects	USA	Mean age in AF patients: 74 m; 76 f (range 55-94 in AF)	maximum 40 years	Study began in 1948	All cause mortality.	Original Framingham Heart Study cohort (longitudinal, population-based); age 28-62 at entry.
Ruigomez, 2002	Study examines mortality rate of patients recently diagnosed with AF and compares it against the general UK population. Adjusted relative risk of death in the AF cohort was 2.5 compared to general population.	Survival probability was computed in both cohorts and the relative risk of dying associated with AF was estimated using Cox prop. hazard regression to control for risk factors.	1,035	UK	NR	Average 2y	Diagnosis made in 1996, end of follow up December 1999.	all-cause and cause-specific mortality	Using GPRD data, patients aged 40–89 years with a first diagnosis of permanent/chronic atrial fibrillation in 1996 were identified. Using the same source population as for the AF cohort, an age and sex matched cohort of 5,000 individuals free of AF was sampled.
Miyasaka, 2007	Mortality risk in patients recently diagnosed with AF was high, especially in the first months after diagnosis, after which mortality seems to plateau. No evidence of significant changes in terms of overall/early/late mortality in 21 years in patients without preexisting CVD.	Cumulative survival after AF was estimated using the KM method. Observed and expected mortality were plotted and compared using the log-rank test	4,618	USA	73 (sd 14 years)	Mean follow up 5.3 (sd 5y); max 24 years.	Diagnosis made between 1980 and 2000. End of follow-up 2004 or death.	ACM	Community based cohort of residents of Olmsted County, Minnesota with ekg confirmed AF.

Miyasaka 2007



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Heart Rhythm Disorders

Mortality Trends in Patients Diagnosed With First Atrial Fibrillation

A 21-Year Community-Based Study

Yoko Miyasaka, MD, PHD, FACC,* Marion E. Barnes, MSC,* Kent R. Bailey, PHD,†
Stephen S. Cha, MS,† Bernard J. Gersh, MB, CHB, DPHIL, FACC,* James B. Seward, MD, FACC,*
Teresa S. M. Tsang, MD, FACC*

Rochester, Minnesota

Relative to the age- and gender-matched general Minnesota population, the mortality risk was increased (p 0.0001) with a hazard ratio (HR) of 9.62 (95% confidence interval [CI] 8.93 to 10.32) within the first 4 months and 1.66 (95% CI 1.59 to 1.73) thereafter.

Miyasaka 2007

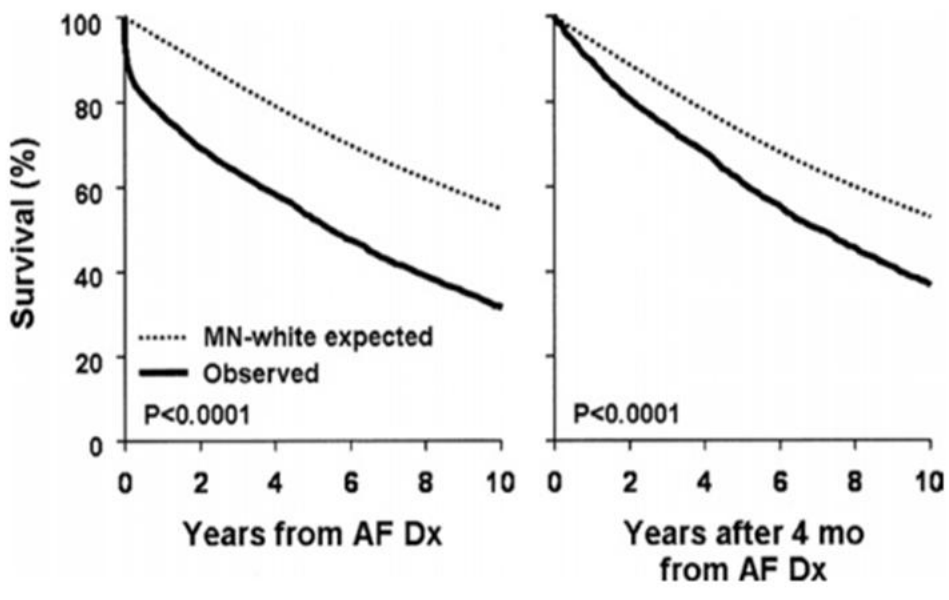


Figure 1 **Survival for AF Patients Compared With the Age- and Gender-Matched General MN Population**

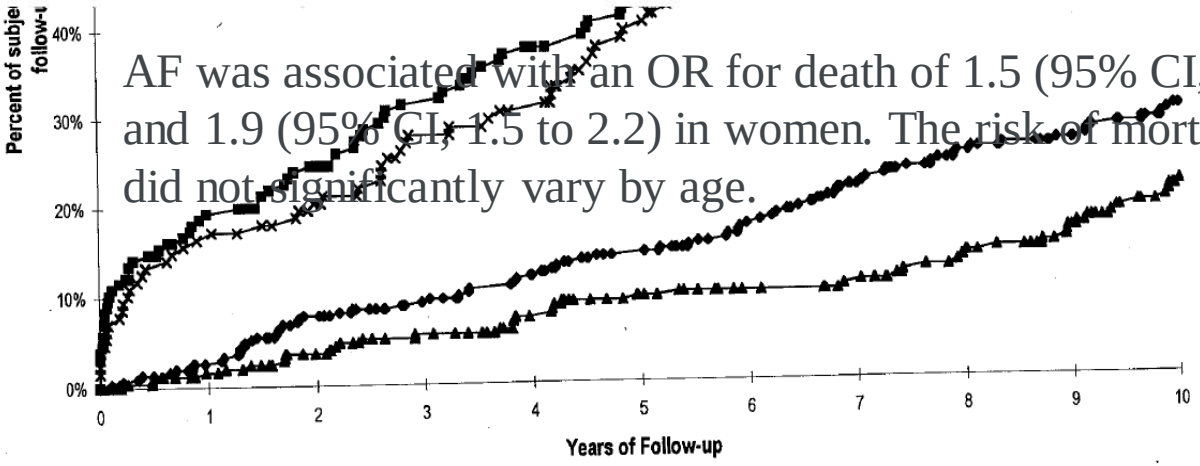
Survival for the entire study population of patients diagnosed with first atrial fibrillation (AF) **(left)** and for the subgroup of survivors who lived beyond the first 4 months after the initial AF diagnosis (Dx) **(right)**, compared with the age- and gender-matched general Minnesota (MN) population.

Benjamin 1998 Framingham

Clinical Investigation and Reports

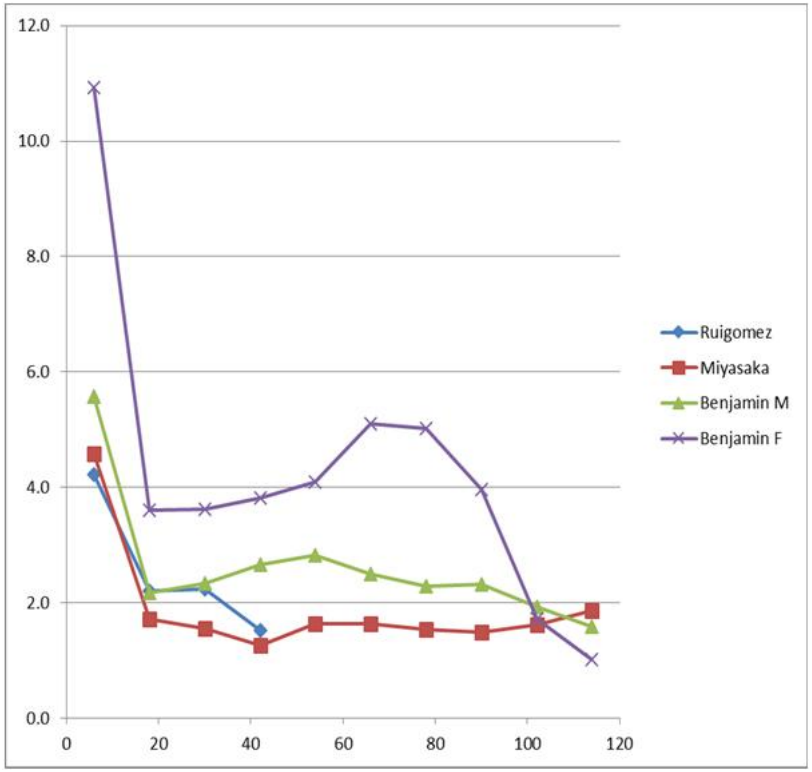
Impact of Atrial Fibrillation on the Risk of Death
The Framingham Heart Study

Emelia J. Benjamin, MD, ScM; Philip A. Wolf, MD; Ralph B. D'Agostino, PhD;
Halit Silbershatz, PhD; William B. Kannel, MD; Daniel Levy, MD

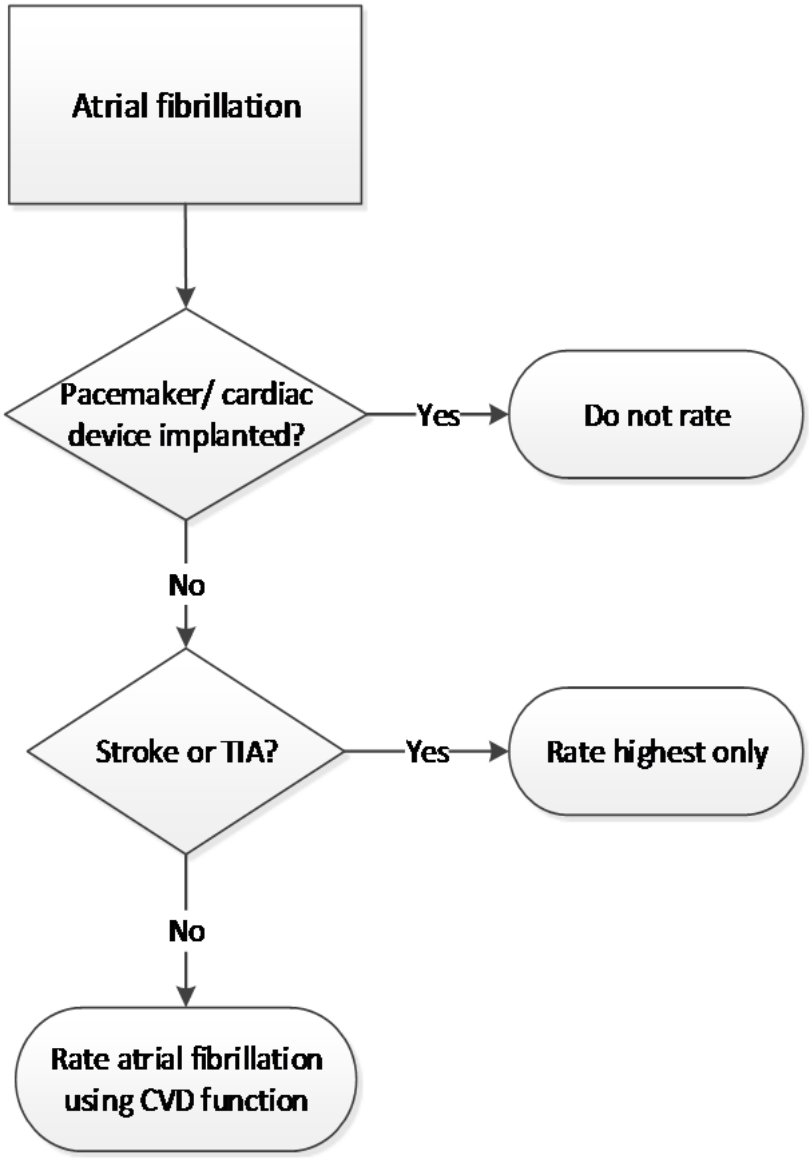


AF was associated with an OR for death of 1.5 (95% CI, 1.2 to 1.8) in men and 1.9 (95% CI, 1.5 to 2.2) in women. The risk of mortality conferred by AF did not significantly vary by age.

Summary risks of AF

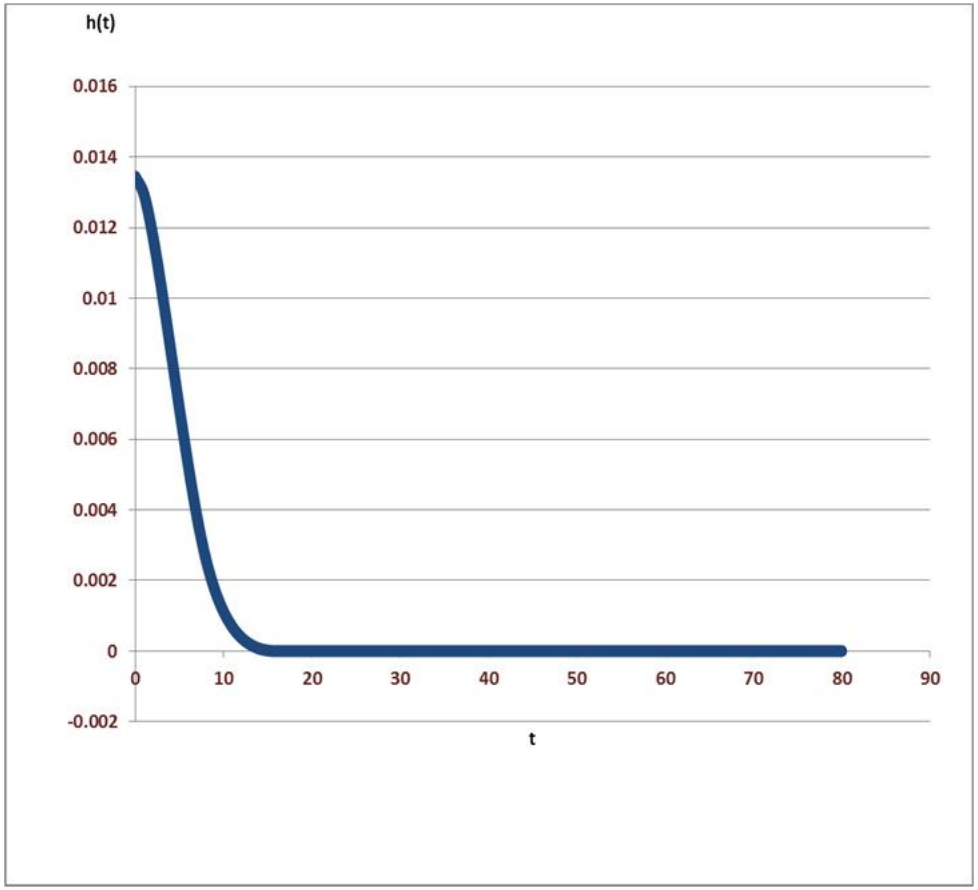


AF: decision tree



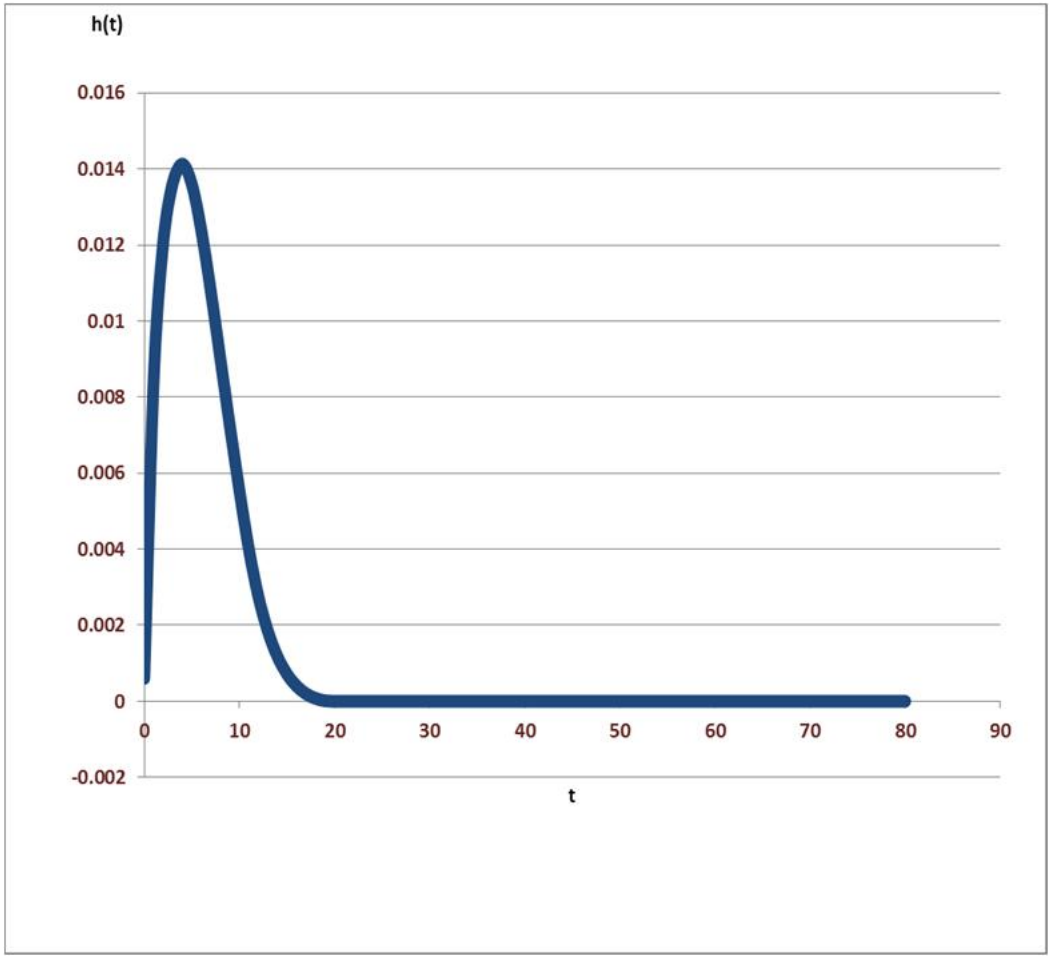
Breast Cancer

Inputs	
Age At Diagnosis	62.43
Current Age	66.50
Gender	Female
Stage	2
Grade	1
Oestrogen Receptor	Negative
Born date	13/12/1946
Diagnosis date	17/05/2009
Policy Date	14/06/2013



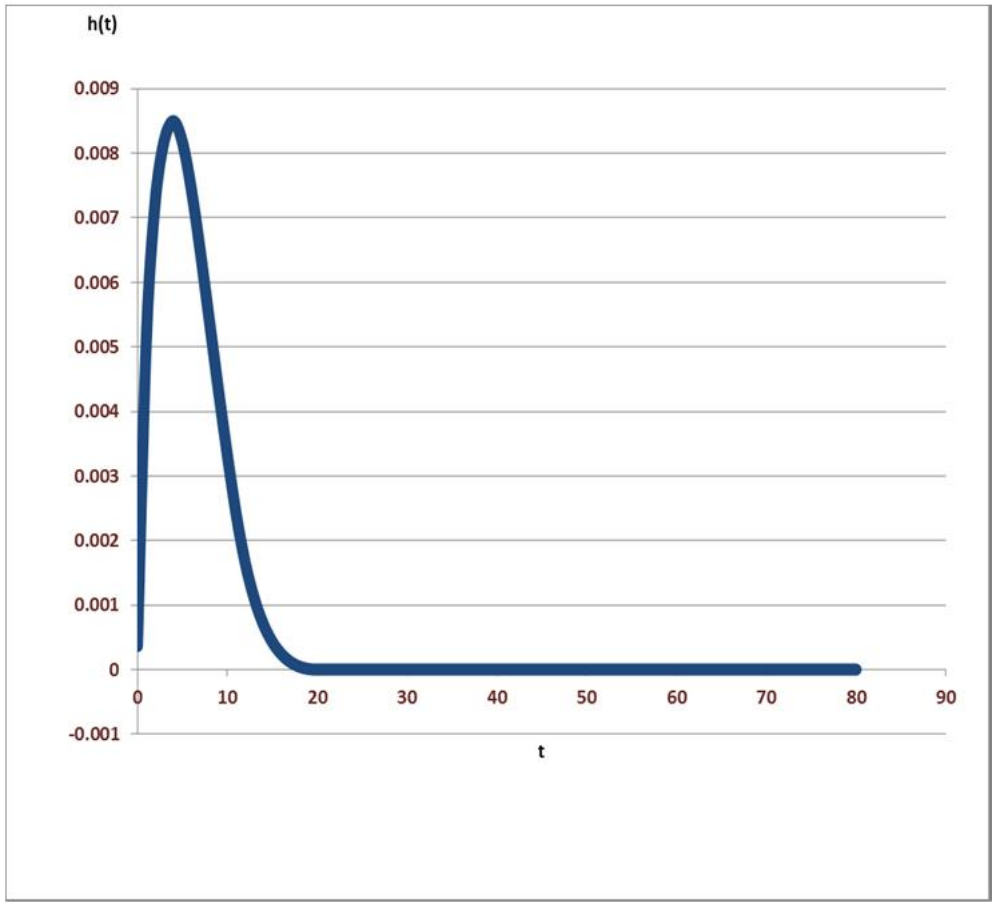
Breast Cancer

Inputs	
Age At Diagnosis	66.43
Current Age	66.50
Gender	Female
Stage	2
Grade	1
Oestrogen Receptor	Negative
Born date	13/12/1946
Diagnosis date	17/05/2013
Policy Date	14/06/2013



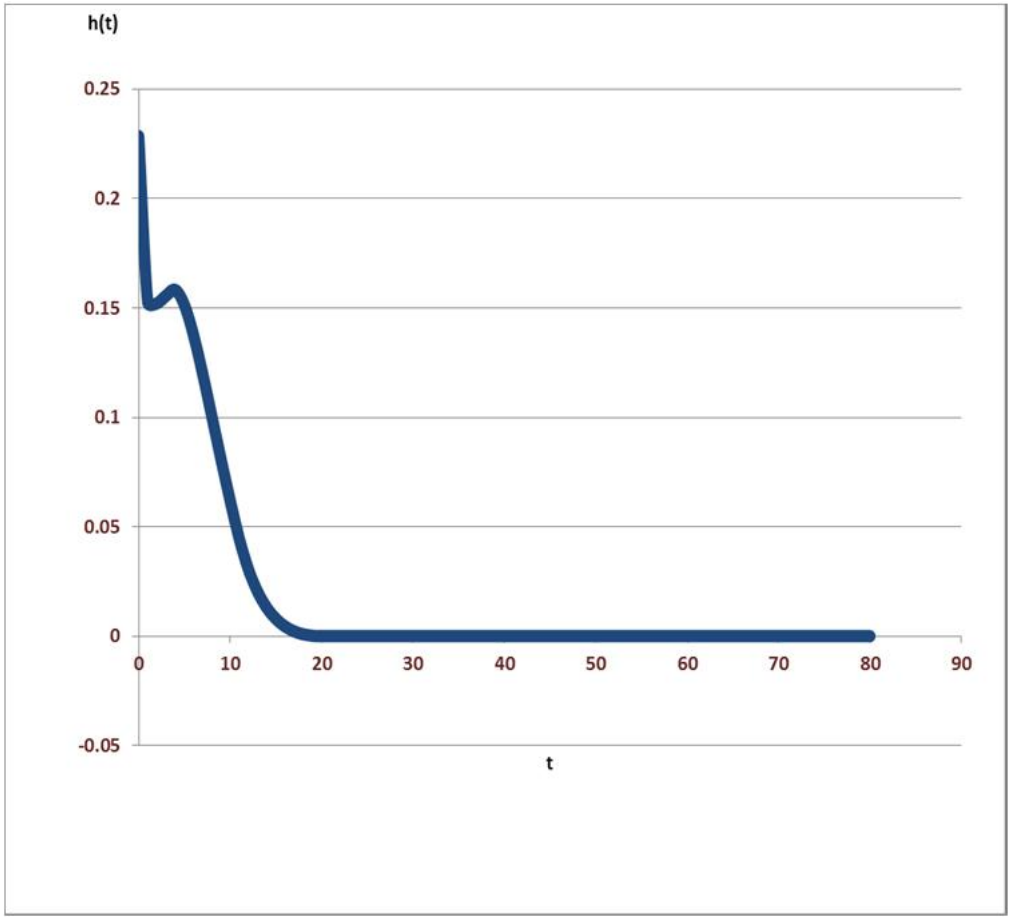
Breast Cancer

Inputs	
Age At Diagnosis	66.43
Current Age	66.50
Gender	Female
Stage	2
Grade	1
Oestrogen Receptor	Positive
Born date	13/12/1946
Diagnosis date	17/05/2013
Policy Date	14/06/2013



Breast Cancer

Inputs	
Age At Diagnosis	66.43
Current Age	66.50
Gender	Female
Stage	4
Grade	2
Oestrogen Receptor	Positive
Born date	13/12/1946
Diagnosis date	17/05/2013
Policy Date	14/06/2013



Demonstration of PrognoSys

PrognoSys™

- Framework to knit together evidence from diverse sources into a coherent set of functions that describe human mortality
- Uses a large variety of functions, from flexible parametric, splines, Markov models, bespoke deterministic
- Interactions
- COPD
- Bowel cancer

Further reading and contact details

Diabetologia (2004) 47:1747–1759
DOI 10.1007/s00125-004-1527-z

Diabetologia

A model to estimate the lifetime health outcomes of patients with Type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68)

P. M. Clarke[1, 4] · A. M. Gray[1] · A. Briggs[1] · A. J. Farmer[2] · P. Fenn[3] · R. J. Stevens[4] · D. R. Matthews[5]
I. M. Stratton[4] · R. R. Holman[4] · on behalf of the UK Prospective Diabetes Study (UKPDS) Group

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[2] Department of Primary Health Care, University of Oxford, UK
[3] Business School, University of Nottingham, UK
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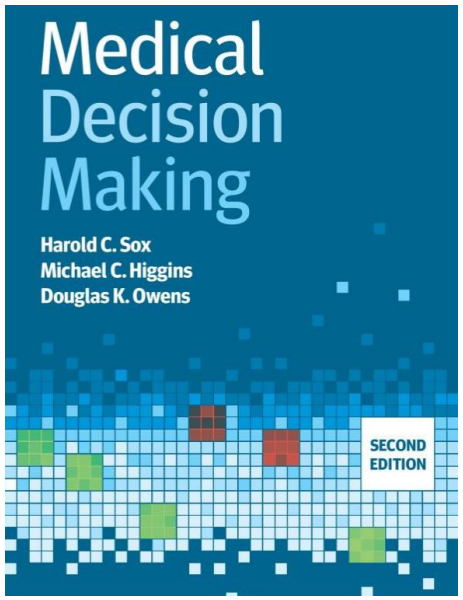
[5] Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Oxford, UK

SIAS
Staple Inn Actuarial Society

Disease and Death

Improving our understanding of the future

by
Hande Love and Daniel Ryan



The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Explaining the Decrease in U.S. Deaths from Coronary Disease, 1980–2000

Earl S. Ford, M.D., M.P.H., Umed A. Ajani, M.B., B.S., M.P.H., Janet B. Croft, Ph.D., Julia A. Critchley, D.Phil., M.Sc., Darwin R. Labarthe, M.D., M.P.H., Ph.D., Thomas E. Kottke, M.D., Wayne H. Giles, M.D., M.S., and Simon Capewell, M.D.

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