Developing a lifetime risk-calculator using the UKPDS risk engine

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1 Lifetime risk model

1.1 Competing risks model

The UKPDS risk engine has been developed for both coronary heart disease (CHD) and Stroke separately (Stevens et al., 2001; Kothari et al., 2002). Both engines give the risk of an event occurring over the next t years in the absence of death from causes other than the event under consideration. We use the risk equations developed in these engines (specifically the cumulative hazard functions) within a competing risks framework to obtain lifetime risks of CVD. Specifically, we assume that only one of the following competing risks can occur:

- 1. CHD;
- 2. Stroke;
- 3. Non-CVD related mortality.

In a competing risks model, cause-specific hazards are summed to obtain the overall hazard of an event occurring (in this case either CHD, Stroke or Non-CVD related mortality). Defining $h_i(t)$ to be the cause-specific hazard for cause i ($i = 1$ CHD, $i = 2$ Stroke, $i = 3$ Non-CVD mortality), then the overall hazard of an event occurring is

$$h(t) = \sum_{i=1}^{3} h_i(t).$$

The cumulative hazard function is defined as

$$H(t) = \int_0^t h(u)\, du = \sum_{i=1}^{3} \int_0^t h_i(u)\, du = \sum_{i=1}^{3} H_i(t),$$

and the probability of an event occurring by time t is then defined in terms of the cumulative hazard function as

$$R(t) = 1 - \exp(-H(t)), \tag{1}$$

which is one minus the survival function.

1.2 UKPDS cause-specific hazards

The UKPDS risk models for CHD (Stevens et al., 2001) and Stroke (Kothari et al., 2002) are expressed in the form shown in Equation 1 as Gompertz survival models and hence, using the notation in the papers, we obtain the cumulative cause-specific hazard functions for a set of risk factors $x = \{T, AGE, SEX, AC, SMOK, H, SBP, LR, AF\}$, which are summarised in Table 1. For cause i (CHD=1, Stroke=2) the cumulative cause-specific hazard after t years is:

$$\begin{aligned} H_i(t|x) &= q_i d_i^{T_i} \left(\frac{1-d_i^t}{1-d_i} \right) \\ \text{(CHD): } q_1 &= q_{01} \beta_{11}^{AGE-55} \beta_{21}^{SEX} \beta_{31}^{AC} \beta_{41}^{SMOK} \beta_{51}^{H-6.72} \beta_{61}^{(SBP-135.7)/10} \beta_{71}^{ln(LR)-1.59} \\ \text{(Stroke): } q_2 &= q_{02} \beta_{12}^{AGE-55} \beta_{22}^{SEX} \beta_{42}^{SMOK} \beta_{62}^{(SBP-135.5)/10} \beta_{72}^{LR-5.11} \beta_{82}^{AF}. \end{aligned}$$

The intercept parameters q_{0i}, and hazard ratios d_i and β_{ki} are shown in Table 1 for the variables included in the model. Note that some variables only affect the risk of one of the events.

Risk Factor	Abbreviation	Estimates		
		Parameter	CHD	Stroke
Intercept		q_{0i}	0.0112	0.00186
Duration of diagnosed diabetes, per year	T	d_i	1.078	1.145
Age at diagnosis of diabetes, per year	AGE	β_{1i}	1.059	1.145
Female sex	SEX	β_{2i}	0.525	0.700
Afro-Caribbean ethnicity	AC	β_{3i}	0.390	-
Smoking at diagnosis of diabetes	SMOK	β_{4i}	1.350	1.547
HbA_{1c} (%)	H	β_{5i}	1.183	-
Systolic blood pressure, per 10mmHg increase	SBP	β_{6i}	1.088	1.122
Lipid ratio	LR	β_{7i}	3.845[1]	1.138
Atrial Fibrilation	AF	β_{8i}	-	8.554

Table 1: Parameter estimates from UKPDS CHD and Stroke risk engines.

1.3 Non-CVD mortality cause-specific hazard

Non-CVD related mortality rates are obtained from National Statistics for the year 2010 in England and Wales. These are assumed to apply to a population of non-smokers. To increase the non-CVD mortality rate for current smokers, we multiply these rates by 2.61 for males and 2.49 for females; relative risks obtained from a prospective cohort study of 23,560 men and 25,122 women in Norway (Bjartveit and Tverdal, 2006). The figures used are adjusted relative risks for sustained smokers versus sustained never smokers and relate to all-cause mortality. However, we assume the relative risks apply similarly for non-CVD related mortality, as verified by comparing unadjusted relative risks for all-cause and non-CVD related mortality in the publication (Table 3 of Bjartveit and Tverdal (2006)).

[1] one unit increase in logorithm of LR

1.4 Calculating lifetime risks

To calculate lifetime risks we follow the 'life-table' approach of Ulrich et al. (2000) and as described in the JBS III risk engine document [REF]. Specifically, time is divided into 3 month periods, $t = 0, \frac{1}{4}, \frac{1}{2}, \frac{3}{4}, 1, \ldots, 65$, where t is measured in years and $t = 0$ refers to the current date. Each individual provides a set of risk factors (Table 1) from which the following quantities are calculated:

- $a_t = e^{-H_1(t)-H_2(t)} - e^{-H_1(t-\frac{1}{4})-H_2(t-\frac{1}{4})}$: the risk of a CVD-event in interval $(t - \frac{1}{4}, t]$, given CVD-free survival up to $t - \frac{1}{4}$.
- b_t: the risk of a non-CVD death in interval $(t - \frac{1}{4}, t]$, given CVD-free survival up to $t - \frac{1}{4}$.

From these two quantities all else follows. The life table begins at the current time $t = 0$, and the following quantities are calculated:

Quantity	Value at $t = 0$	Value at $t > 0$
Risk of CVD event in interval	0	a_t
Risk of non-CVD death in interval	0	b_t
Proportion of original cohort having non-CVD death in interval	0	$c_t = e_{t-1}b_t$
Proportion of original cohort having CVD event in interval	0	$d_t = e_{t-1}a_t$
Proportion of original cohort surviving free of CVD at end of interval	1	$e_t = e_{t-1} - c_t - d_t$
Cumulative proportion with CVD events by end of interval	0	$f_t = f_{t-1} + d_t$
Cumulative proportion dying from non-CVD causes by end of interval	0	$m_t = m_{t-1} + c_t$

Note that $e_t + f_t + m_t = 1$ for all t.

2 Incorporating intervention effects

Interventional effects of a risk factor (i.e. how the ratio of daily risks change before and after an applied intervention *in the same person*) are required to show effects of behavioural and lifestyle changes on lifetime risks. These effects may be quite different from 'epidemiological' risks, like those shown in Table 1, which calculate the ratio of daily risks in two different people who differ in the specified risk factor. Interventional effects are usually measured from longitudinal studies, with randomised controlled trials (RCTs) designed to change the risk factor of interest being the gold standard, since randomisation should on average ensure other confounding variables are balanced between the intervention arms. A number of interventional changes are of interest, and here we list the evidence obtained for each. Caution is required for some of the interventions where the evidence is weak and strong assumptions must be made.

2.1 HbA_{1c}

The UKPDS blood-glucose control RCT compared an intensive blood-glucose control policy (using sulphonylureas or insulin) with a conventional dieting policy. In this trial

the intervention group had consistently lower HbA_{1c} over follow-up (7.0% vs 7.9% at 10 years). The relative risk of myocardial infarction was decreased (RR=0.84 95%CI 0.71, 1.00) but there was little evidence of an effect on stroke. For a 1% decrease in HbA_{1c} we therefore assume a 0.845 decrease in the hazard of CHD, but no effect on Stroke. This estimate is used directly in the UKPDS risk engine, and is broadly similar to the trial results and those reported in other studies (Boussageon et al., 2011) (Table 2).

2.2 Blood pressure

The UKPDS 38 RCT (Group, 1998) compared tight blood pressure control (using an angiotensin converting enzyme inhibitor captopril or a β blocker atenolol) with less tight control. After nine years of follow-up the mean difference in systolic blood pressure between the randomised groups was 10mmHg (95%CI 9, 12). The relative risk reduction in Stroke for patients in the tight blood pressure control arm was 0.56 (95%CI 0.35, 0.89), but there was insufficient evidence to find a significant reduction in Myocardial infarction. We therefore use the relative risk figure as the interventional effect on Stroke for a 10mmHg decrease in systolic blood pressure, whilst we assume no effect on Myocardial infarction.

2.3 Lipid lowering

Evidence for the interventional effect of lowering cholesterol comes from the Cholesterol Treatment Trialists' (CTT) Collaboration, which conducted a meta-analysis of 14 randomised trials of statins in people with and without diabetes (Cholesterol Treatment Trialists' (CTT) Collaborators et al., 2008). Among participants with diabetes, there was a significant 21% proportional reduction (0.79 95%CI 0.77, 0.81) in the incidence of major vascular events per mmol/L LDL cholesterol reduction. We use this figure directly as an interventional effect of LDL cholesterol reduction, transforming total and HDL cholesterol, as entered by the user, to LDL cholesterol by using the formulae $LDL \approx (Total - HDL)/1.24$ [REF Robinson].

2.4 Smoking

An observational study conducted in Norway collected data on smoking patterns at two consecutive examinations in order to define never-smokers, sustained ex smokers, sustained smokers and quitters (Bjartveit and Tverdal, 2006). The adjusted relative risk of CVD mortality was compared across the smoking categories, with sustained never smokers as the reference category. To calculate an intervention effect we take the ratio of relative risks in those that stopped smoking between the examinations ('quitters') to those who were sustained smokers. Hence the relative risk reduction associated with quitting for CVD mortality is $1.55/2.99 = 0.52$ in men and $1.93/3.99 = 0.48$ in women. These sex-specific figures are assumed to apply to the reduction in risk of all CVD events, not just mortality.

The adjusted relative risk of all-cause mortality in 'quitters' compared with sustained smokers is $1.39/2.61 = 0.53$ in men and $1.64/2.49 = 0.66$ in women. It is assumed these sex-specific figures also apply to the reduction in risk of non-CVD mortality. As a test of this assumption the crude unadjusted relative risks for non-CVD mortality can be calculated from the publication (Table 3 of Bjartveit and Tverdal (2006)) and these are found to be similar to all-cause mortality relative risks (0.57 vs 0.56 in men and 0.70 vs

0.64 in women). In the risk engine the intervention effect of quitting will only be applied if a person is a current smoker but intends to quit.

2.5 Weight loss

The evidence for interventional effects of weight loss on CVD outcomes is limited. Epidemiological effects of lower body mass index (BMI) are reported in a Finnish study of patients with diabetes (Hu et al., 2005) and these effects are used in the risk engine. However, they should be used with caution and could be larger than those seen from an intervention study. The fully adjusted hazard ratio for CVD mortality associated with the third tertile of BMI (Obese, $> 30.4 Kg/m^2$ in men, $> 32.6 Kg/m^2$ in women) compared with the second tertile (Overweight, $27.1 - 30.4 Kg/m^2$ in men, $28.0 - 32.6 Kg/m^2$ in women) is $0.97/1.25 = 0.776$. This is assumed to also apply to all CVD events, not just CVD-related mortality.

2.6 Physical Activity

The Finnish study by Hu et al. (2005) also provides evidence for the effect of physical activity on cardiovascular mortality. We assume that the interventional effect of going from low physical activity (¡4 hours light physical activity per week, e.g. walking, cycling, light gardening) to moderate physical activity (¿4 hours light physical activity per week) is the same as the reported epidemiological adjusted hazard ratio of 0.57. There was no evidence of an effect between moderate and high physical activity groups. This effect is assumed to also apply to all CVD events, not just CVD-related mortality.

Risk Factor	Interventional effect		
	CHD	Stroke	Non-CVD mortality
HbA_{1c}, per 1% decrease	0.845	-	-
Systolic blood pressure, per 10mmHg decrease	-	0.56	-
LDL cholesterol, per mmol/L reduction	0.79	0.79	-
Smoking, quitting	0.52[1] (0.48[2])	0.52[1] (0.48[2])	0.53[1] (0.66[2])
Weight loss, Obese to Overweight	0.776	0.776	-
Physical activity, None/Low to Moderate	0.57	0.57	-

Table 2: Interventional effects (hazard ratios) used in the lifetime risk engine.

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[1]Men
[2]Women

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