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# Stroke Mortality and Morbidity in the UK

Padma Chutoo (PhD candidate)  
University of East Anglia

The **'Use of Big Health and Actuarial Data for understanding Longevity and Morbidity Risks'** research programme is being funded by the Actuarial Research Centre.

30/10/2019

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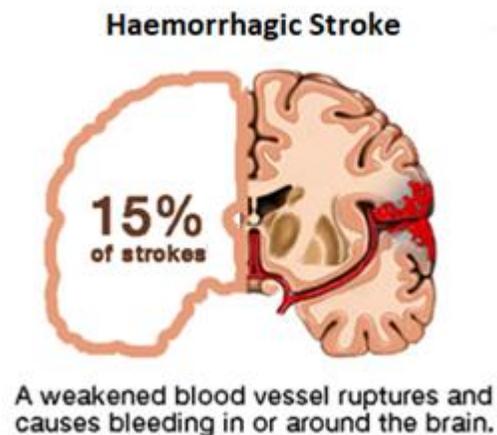
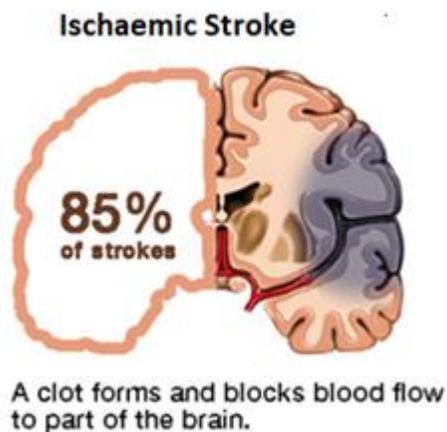
# Overview

- Stroke definition and statistics
- Study description
- Patient Numbers
- Kaplan Meier plots
- Checking the Cox's Proportional hazard Assumption
- Parametric regression fits
- Double Cox-Weibull model specification
- IS model and hazard plots
- Overview of Multiple Imputation
- Future works



# What is Stroke?

- **Ischemic stroke** is caused by a blood clot that blocks or plugs a blood vessel in the brain.
- **Haemorrhagic stroke** is caused by a blood vessel that breaks and bleeds into the brain



- **Transient Ischemic Attacks** or TIAs, are “mini-strokes” whereby the symptoms from the clot appear temporarily. TIAs are warning signs that should be taken seriously.

Source : [medstarhealth.org](http://medstarhealth.org)



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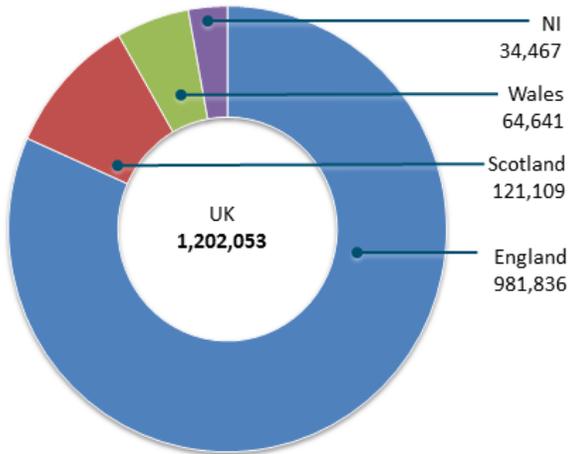
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# Stroke Statistics

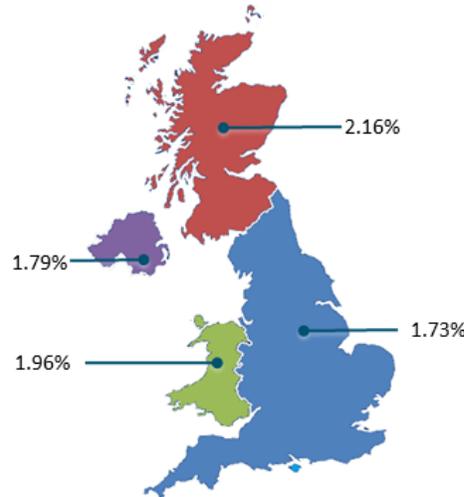
Stroke is the **fourth** single leading cause of death in the UK.



## STROKE SURVIVORS UK



Reference: Health and Social Care Information Centre. Quality and Outcomes Framework (QOF) – 2014-2015.



Stroke is the **biggest single cause of major disability** in the United Kingdom. Almost two-thirds of stroke survivors leave hospital with disability.

Stroke burden is projected to rise from around **38 million** Disability-Adjusted Life Years (DALYs) globally in 1990 to **61 million** DALYs in 2020.



The NHS and social care costs of stroke are around **£1.7 billion** a year in England



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# Stroke study: brief description

- Objective: impact of 1<sup>st</sup> **ischaemic stroke** and **transient ischaemic attack (TIA)** on longevity and morbidity risks.
- The study period is from 1986 up to 2017.
- Design: case/control 1:3
- Exclusion criteria: prior major cancers, dementia, chronic kidney disease stages 3+ and haemorrhagic stroke.
- The primary outcome is all-cause mortality. The secondary outcomes are further strokes, dementia (Alzheimer's and vascular dementia), heart failure, myocardial infarction, pulmonary arterial disease.



# Stroke study: brief description

## Variables of interest:

- **Drugs:** Antihypertensive drugs, Anticoagulant drugs, Lipid regulating drugs and antidiabetic drugs.
- **Medical conditions:** Asthma, Atrial Fibrillation, CKD, CHD, PAD, Hypothyroidism, COPD, Diabetes, Hypercholesterolemia, Hypertension, Depression.
- **Demographical and lifestyle conditions:** Blood-Pressure, Cholesterol, BMI, gender, date of birth, age at entry, smoking status, alcohol status and IMD Decile.



# Patient numbers

## IS dataset

### Full case dataset

( N = 25,711)

Cases = 8,983

Controls = 16,728

## TIA dataset

### Full case dataset

( N = 24,797)

Cases = 9,377

Controls = 15,420

### Multiple Imputation dataset

( N = 75,769)

Cases = 20,250

Controls = 55,519

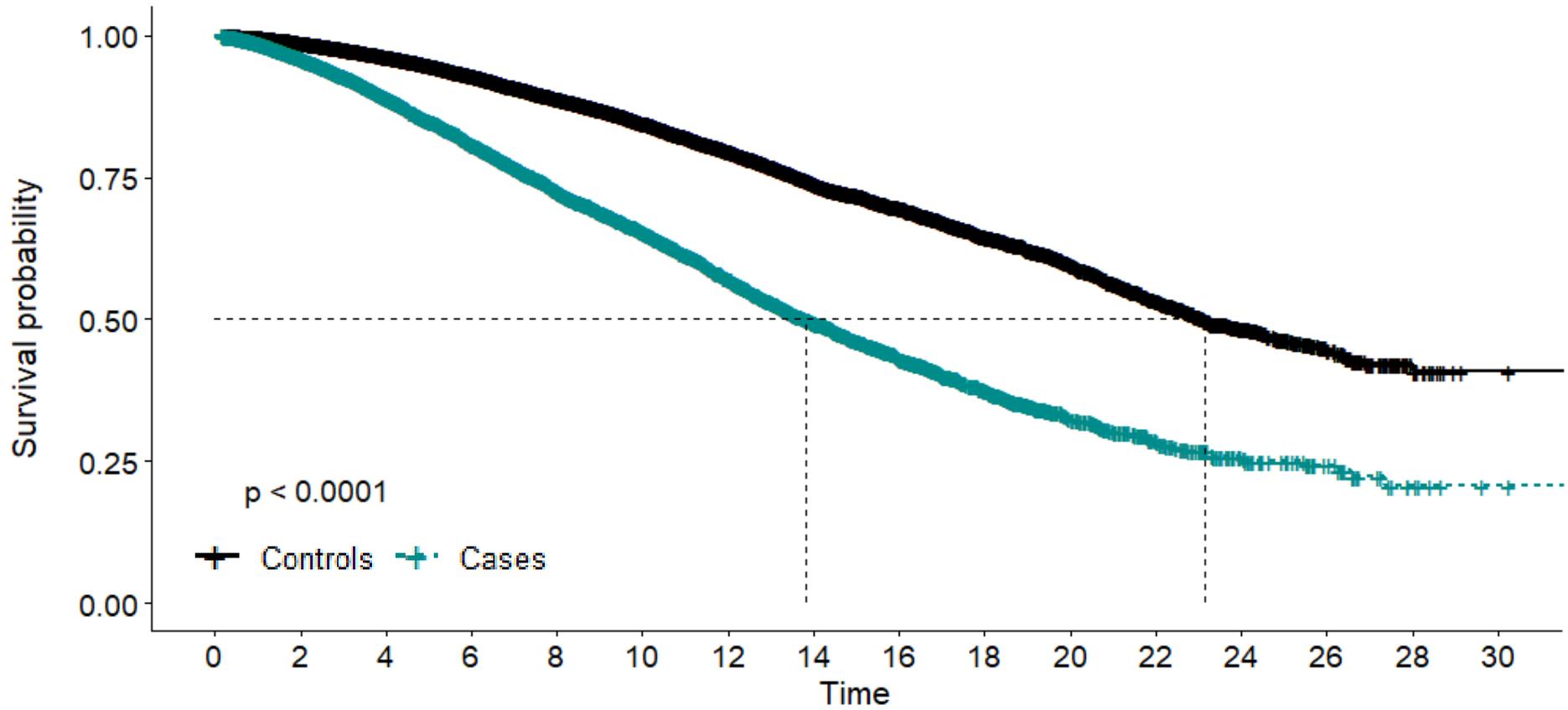
### Multiple Imputation dataset

( N = 74,037)

Cases = 20,633

Controls = 53,374

# Unadjusted Kaplan Meier plot IS cases and controls

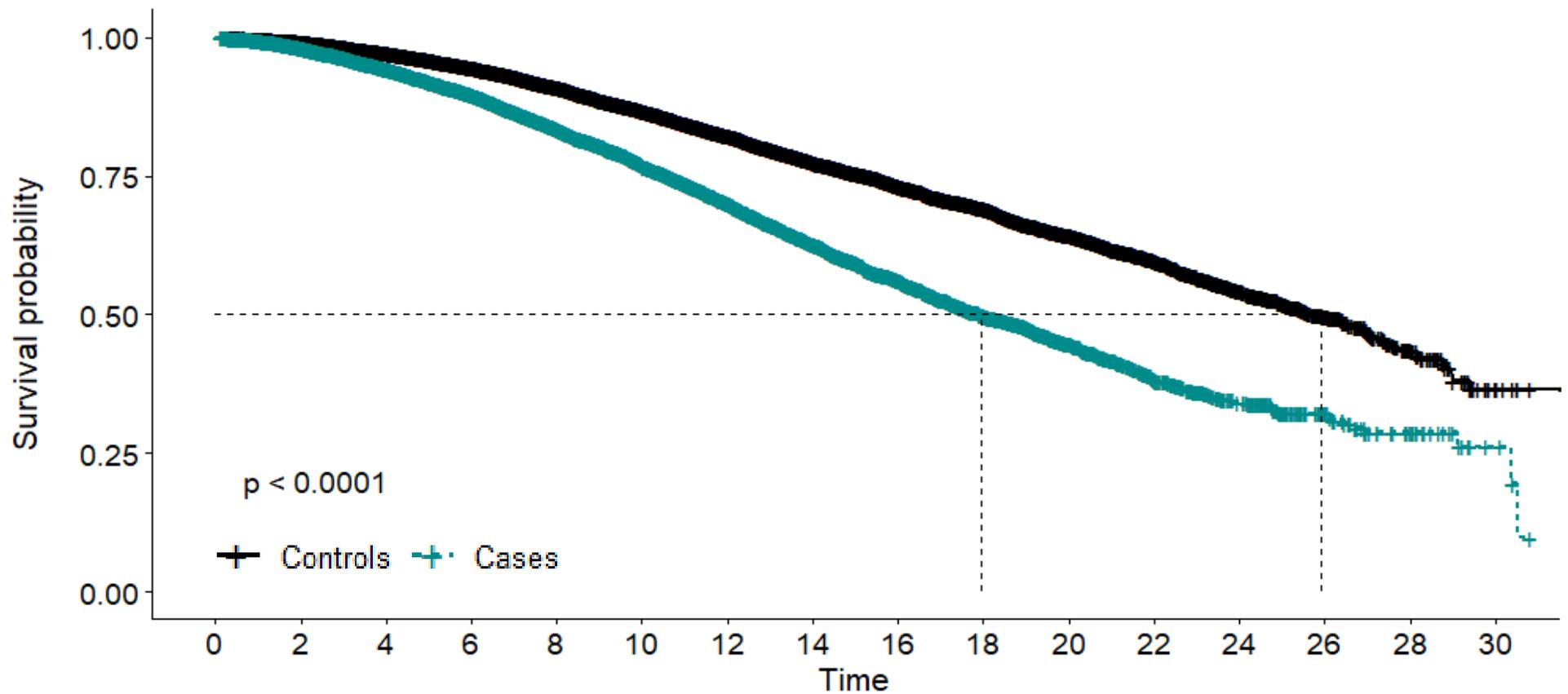


Number at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Controls	16728	15860	13956	11782	9535	7520	5712	4024	2672	1670	1034	607	317	133	31	4
Cases	8983	7997	6451	4963	3724	2748	1941	1255	786	456	235	131	63	29	8	2

Time

# Unadjusted Kaplan Meier plot TIA cases and controls



Number at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Controls	15420	14985	13796	12259	10591	8901	7143	5341	3807	2580	1640	1002	617	264	97	12
Cases	9377	8829	7812	6666	5478	4363	3307	2338	1515	929	565	295	159	60	25	5

## Violations to Cox's Proportional hazard assumption ( $\alpha = 0.05$ )

	rho	chisq	p
birth_cohort1921 to 1930	-0.03057	4.6059	0.03186147087697
birth_cohort1931 to 1940	-0.04986	11.4182	0.00072727164999
birth_cohort1941 to 1960	-0.08358	32.0438	0.00000001507344
age_cat2	0.00991	0.4616	0.49688725441191
age_cat3	-0.01266	0.7385	0.39013103374282
age_cat4	-0.02933	3.9631	0.04650827842605
sexMale	0.00256	0.0294	0.86394990495609
groupscases	-0.03331	4.7344	0.02956567737229
IMD_Quintile2	0.01582	1.2685	0.26005731908003
IMD_Quintile3	0.00982	0.5247	0.46886479768015
IMD_Quintile4	0.02516	3.5033	0.06124845077876
IMD_Quintile5	0.02632	4.0789	0.04342093793658
BMI_catObese	0.03568	5.6952	0.01701099437364
BMI_catOverweight	0.01743	1.3773	0.24055963462973
BMI_catUnderweight	-0.01279	0.7491	0.38677422168589
⋮	⋮	⋮	⋮
AF_factorYes and Treated	-0.00210	0.0205	0.88620238544372
AF_factorYes and Untreated	0.01561	1.1125	0.29153432590237
hypertension_factorYes and Treated	-0.04421	8.7999	0.00301247436989
hypertension_factorYes and Untreated	-0.00589	0.1542	0.69459488132253
age_cat2:groupscases	-0.01262	0.6992	0.40306144688028
age_cat3:groupscases	-0.00481	0.1024	0.74901958328828
age_cat4:groupscases	0.00344	0.0526	0.81864457985083
sexMale:groupscases	0.00573	0.1442	0.70412354400852
groupscases:hypertension_factorYes and Treated	0.02637	3.1294	0.07689249209760
groupscases:hypertension_factorYes and Untreated	0.01609	1.1510	0.28334103952037
GLOBAL	NA	134.1296	0.00000000000228

### Comments

Covariates violating the Cox's PH assumption :  
Birth cohort, Age category, case/control, BMI, IMD, hypertension and antiplatelet.

The global test was highly significant providing evidence of non-proportionality.

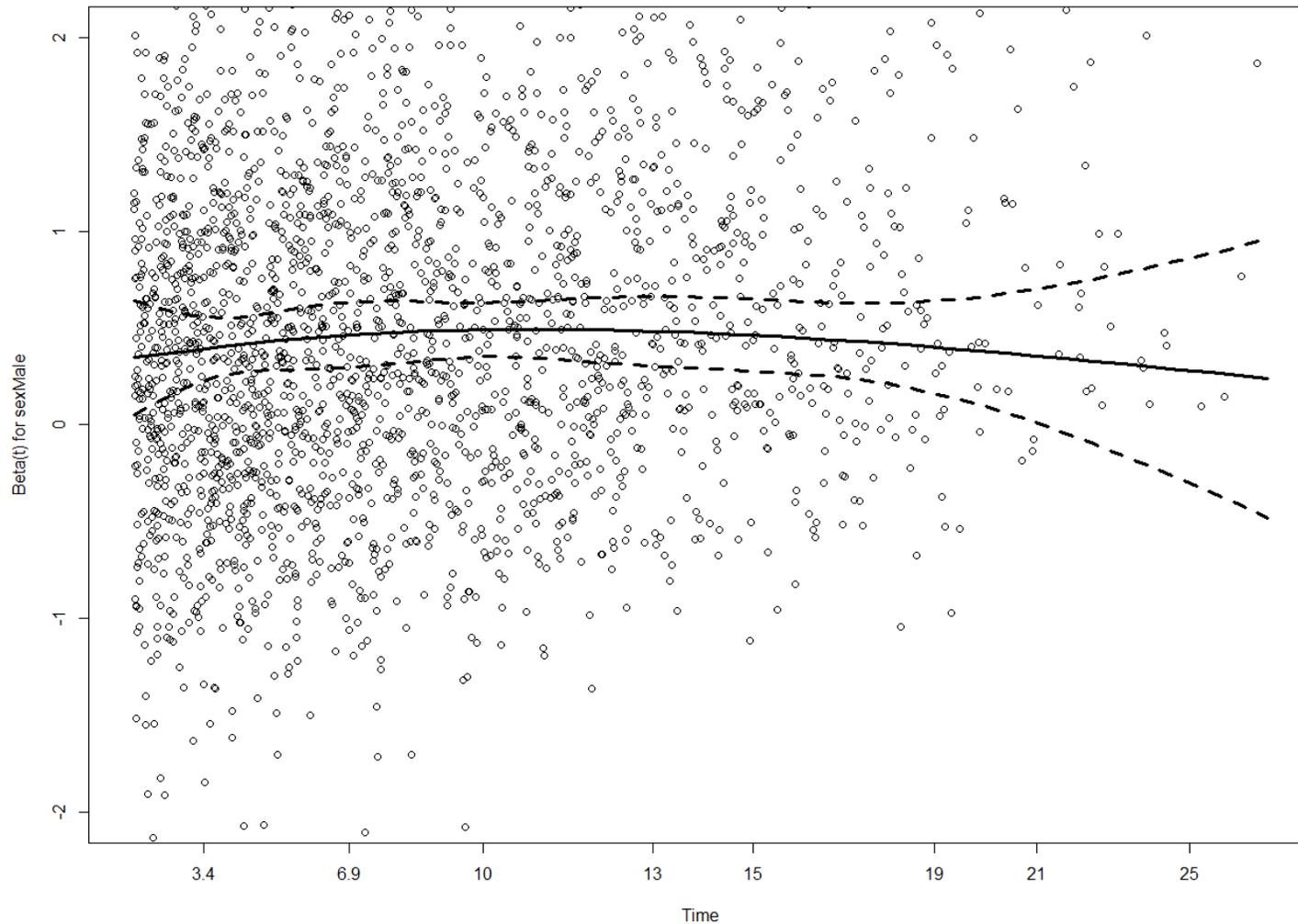


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# Graphical diagnostics based on the scaled Schoenfeld residuals.

## A covariate which does not violate the Cox's PH assumption



### Comments:

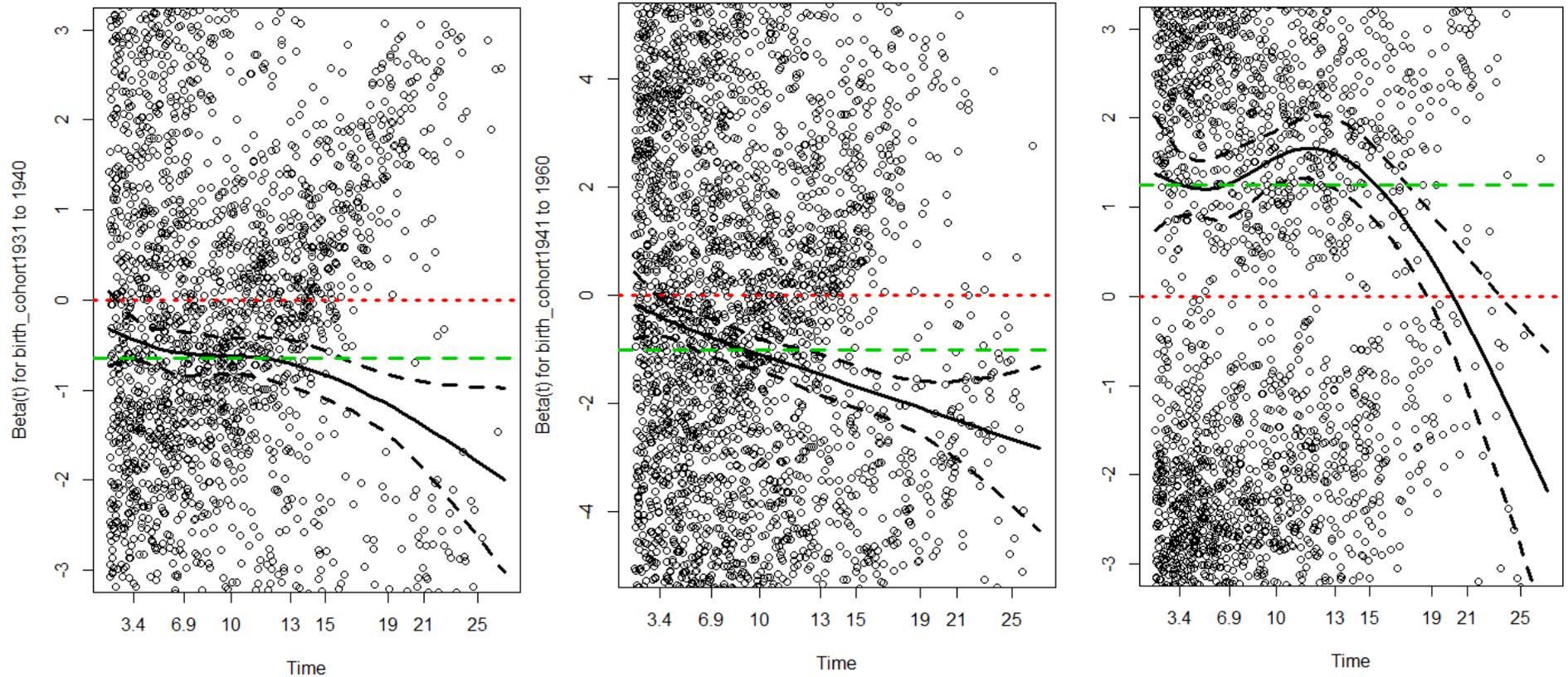
There is no distinct pattern of the residuals with time, so this covariate is not time-dependent.



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# Graphical diagnostics based on the scaled Schoenfeld residuals.



- ..... Reference line for null effect
- - - Average hazard over time
- Time-varying hazard

## Comments:

A non-zero slope is evidence against proportionality.

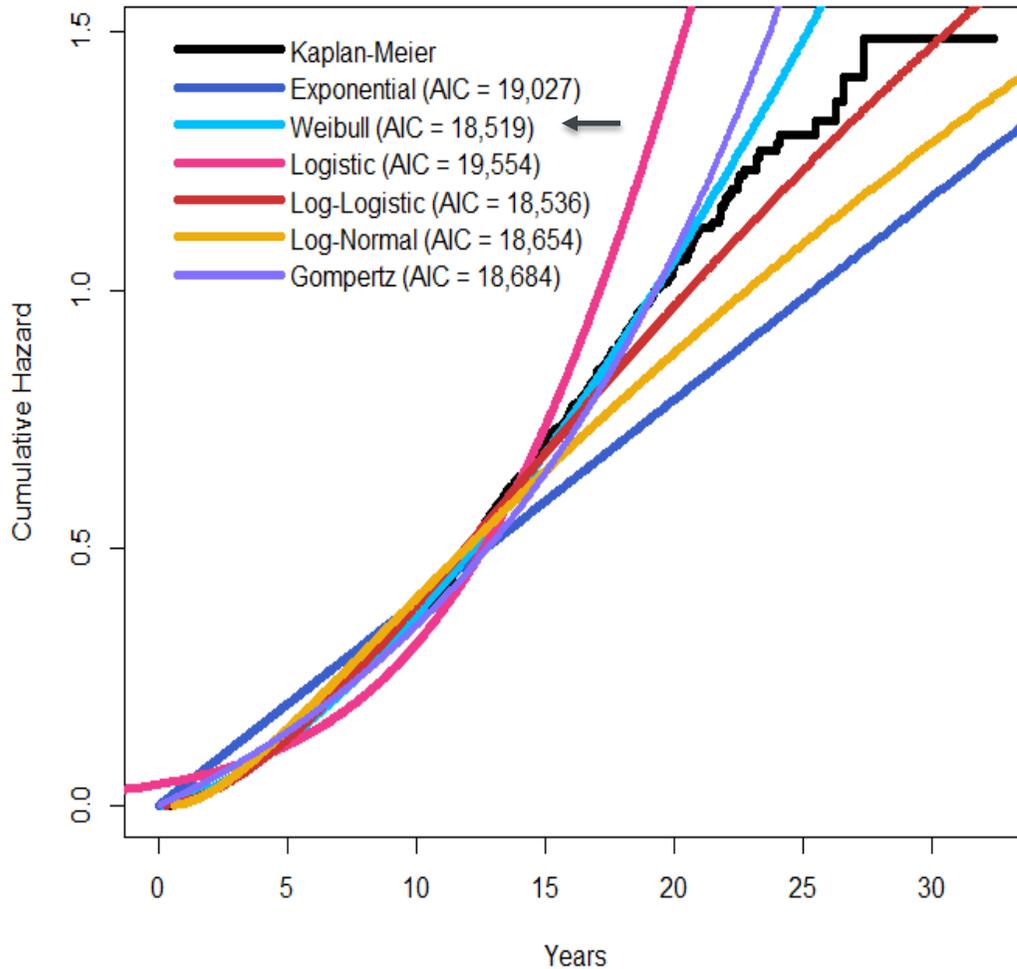


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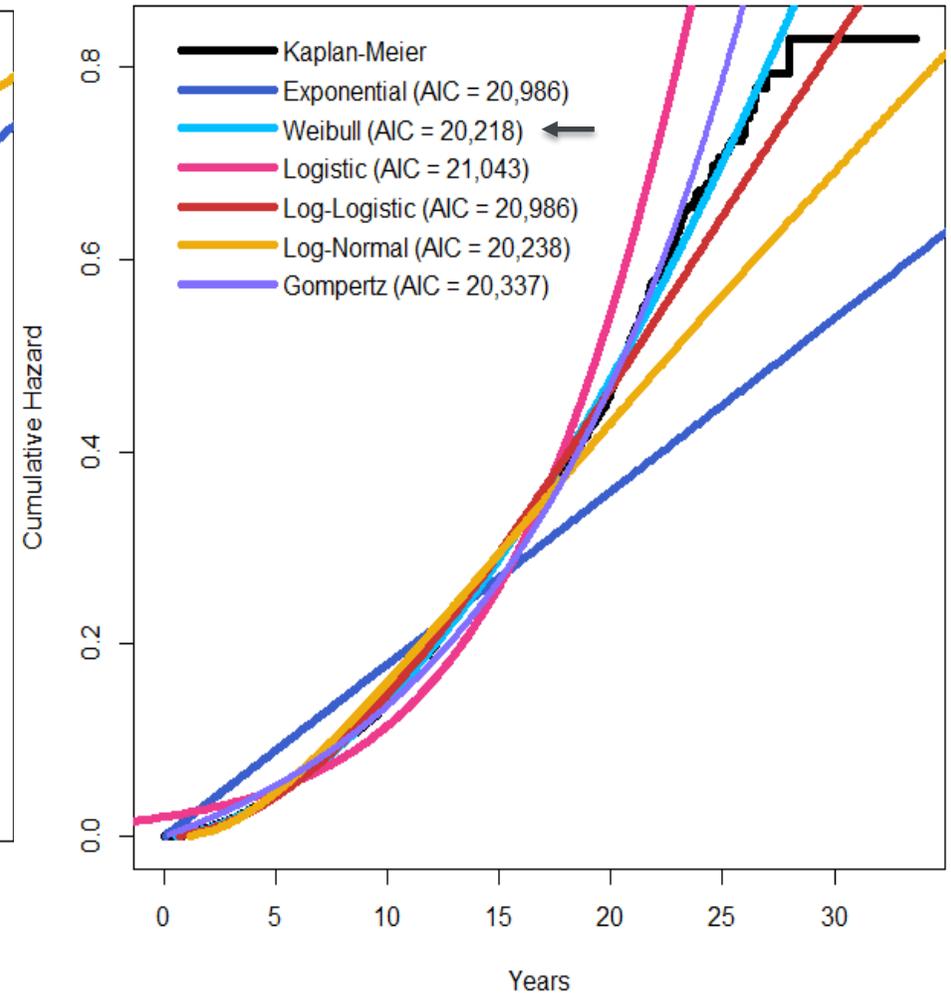
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# Distribution fitting : IS

Parametric Regression Fits  
IS cases



Parametric Regression Fits  
IS controls



# Parametric “Double-Cox” regression

Components:

- A baseline hazard function (which **changes over time**).
- The risk factors  $Z$  have a log-linear contribution to the force of mortality which does not depend on time  $t$ .

The Cox parametric regression model

$$\mu(t|Z) = \mu_0(t|Z) \exp(Z^T \beta)$$

Baseline hazard function

$\beta$  is a vector of unknown parameters for scale and  $Z$  is a vector of covariates

Weibull baseline hazard function with scale  $\lambda$  and shape  $k$ . Shape  $k$  is modelled as  $k=k(Z)$ .

$$\mu_0(t|Z) = \frac{k(Z)}{\lambda} \left(\frac{t}{\lambda}\right)^{k(Z)-1}$$

$$k(Z) = k_0 e^{Z^T \beta_k}$$

Additional regression model to allow varying shape depending on covariates



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# IS model

The scale model includes the following main effects and interactions :

- Birth cohort
- IMD in Quintiles
- Body Mass index
- Antiplatelet therapy
- Chronic Pulmonary Disorder
- Chronic Kidney Disease ( stages 1-3)
- Heart Failure
- Myocardial Infarction
- Peripheral Arterial Disease
- Atrial fibrillation
- Diabetes
- Anticoagulant therapy
- Smoking
- Interaction of IS diagnosis with Antihypertensive treatment
- Interaction of IS diagnosis with sex
- Interaction of IS diagnosis with age

The shape model includes the following main effects :

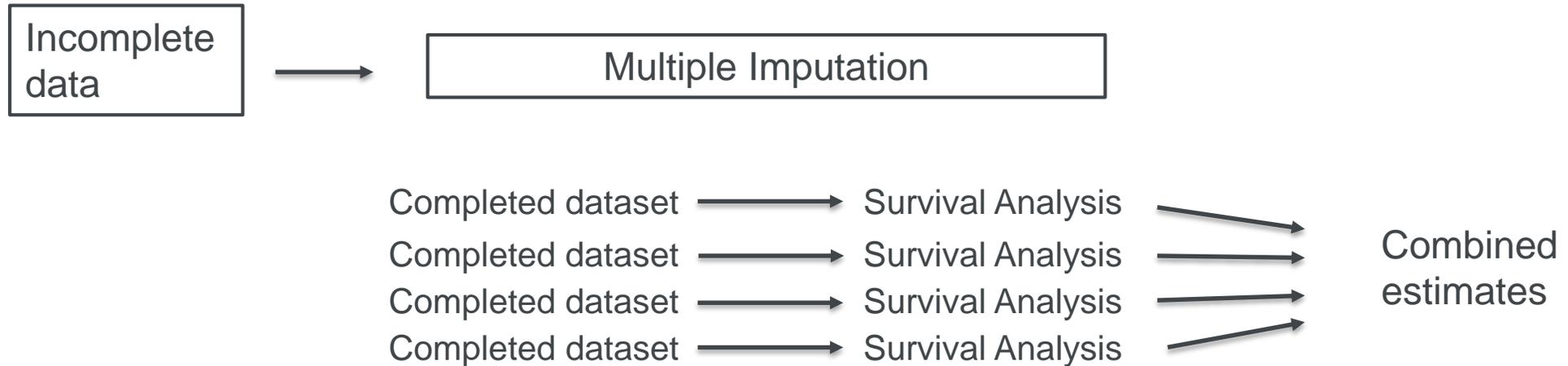
- Birth cohort
- Antiplatelet therapy



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# Overview of Multiple Imputation



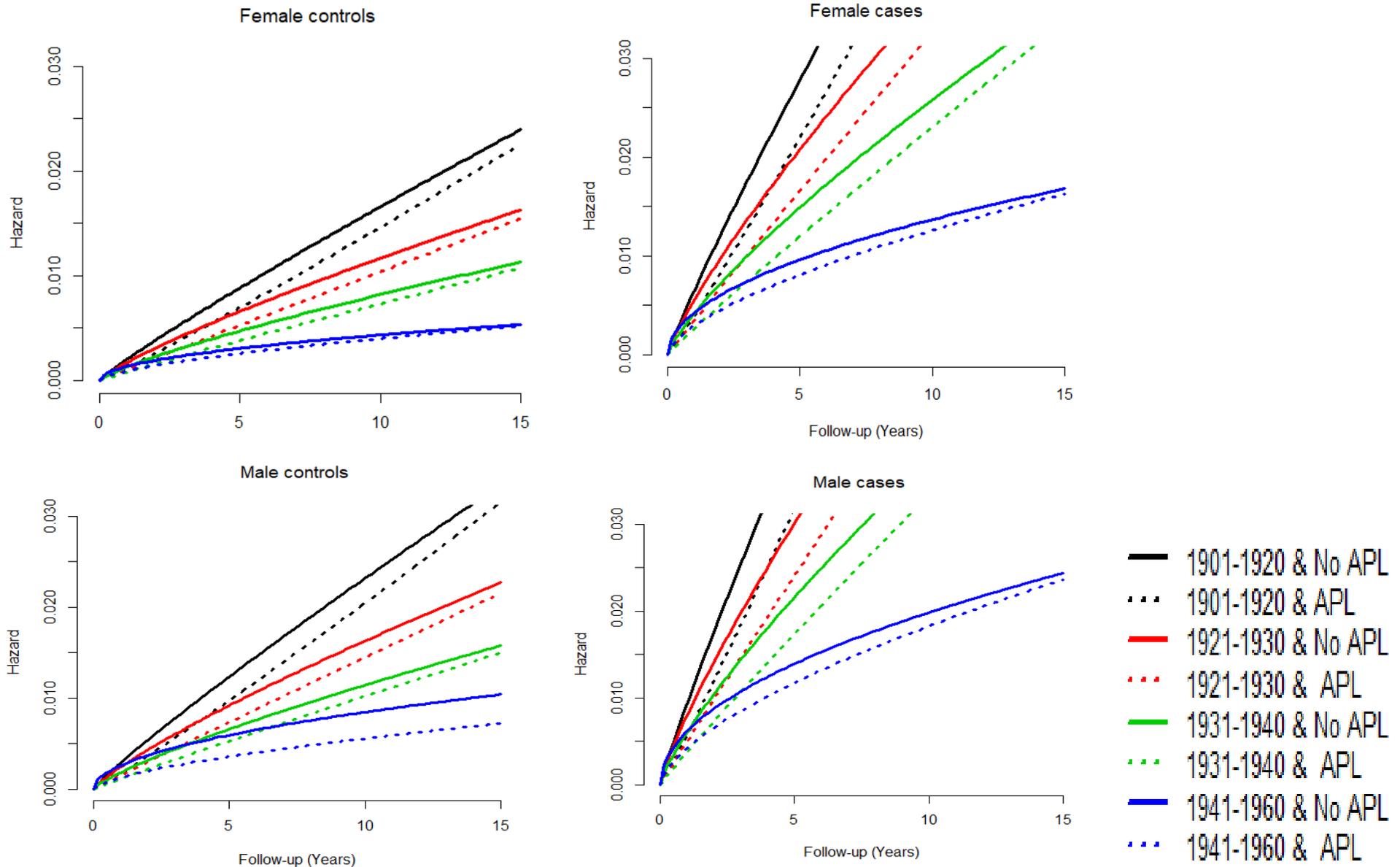
**Step 1 :**  
*Generate multiple sets of imputed values to produce multiple imputed datasets.*

**Step 2 :**  
*Perform survival analysis on each dataset.*

**Step 3 :**  
*Pool the results using Rubin's rules.*



# Hazard curves demonstrating the birth cohort effect : IS

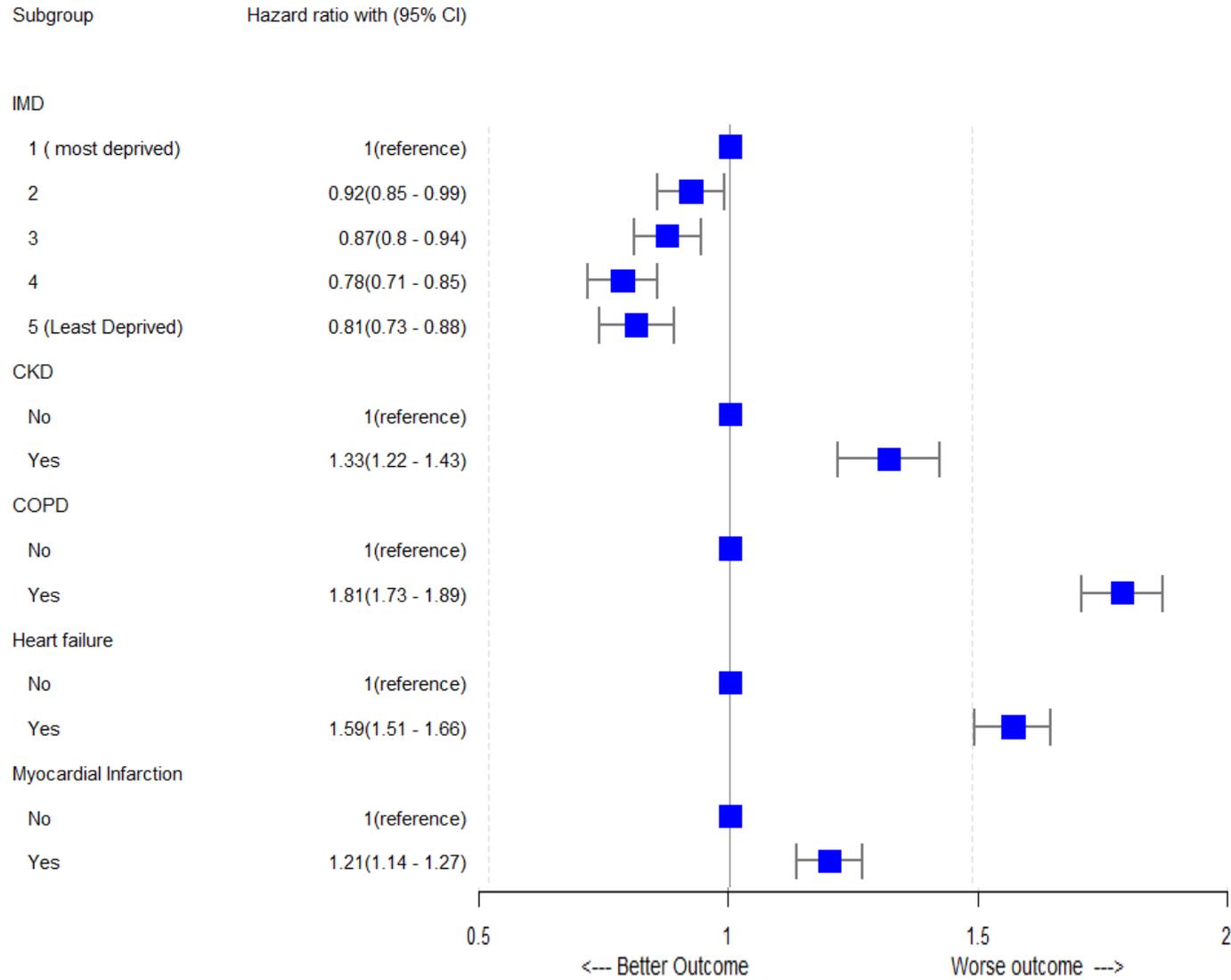


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Hazard curves for healthy cases and controls, aged 39-60 years with IMD Quintile = 1 across different birth cohorts and APL( antiplatelet intake).

# Forest plot : IS

## Adjusted Hazard Ratio

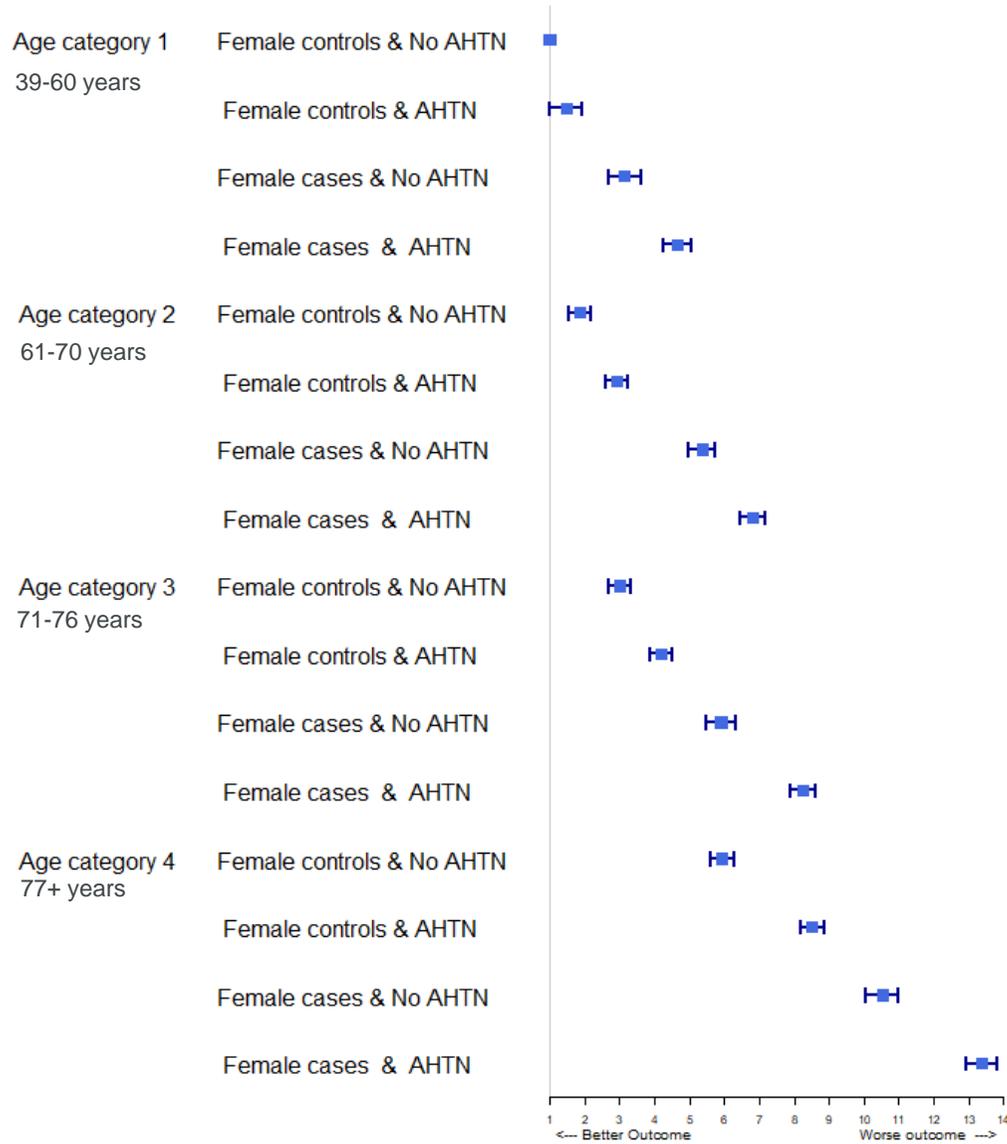


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# Forest plot : IS model

## Adjusted Hazard ratios



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# Future Works:

- Write up two papers: on TIA and on IS
- Translation of models into actuarial analysis



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The **'Use of Big Health and Actuarial Data for understanding Longevity and Morbidity Risks'** research programme is being funded by the ARC.

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