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University of East Anglia

Hormone Replacement Therapy and its effects on Morbidity and Longevity of Women

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Outline

- Brief description of Hormone Replacement Therapy
- Study design and selection criteria
- Distribution of the study population
- Hazards of selected medical conditions at follow-up
- Complete case analysis
- Results

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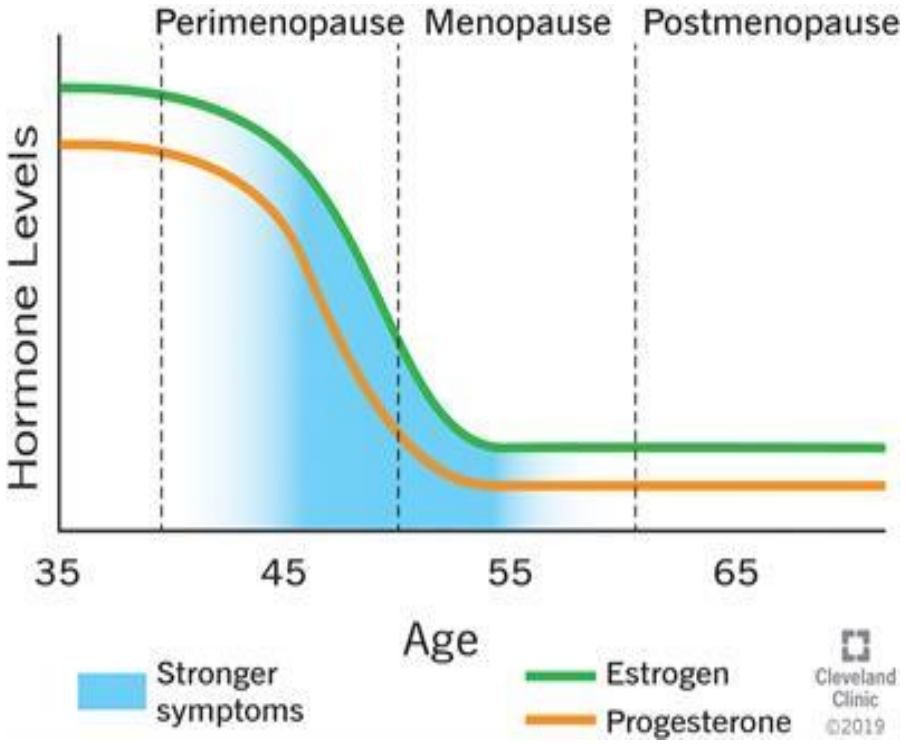
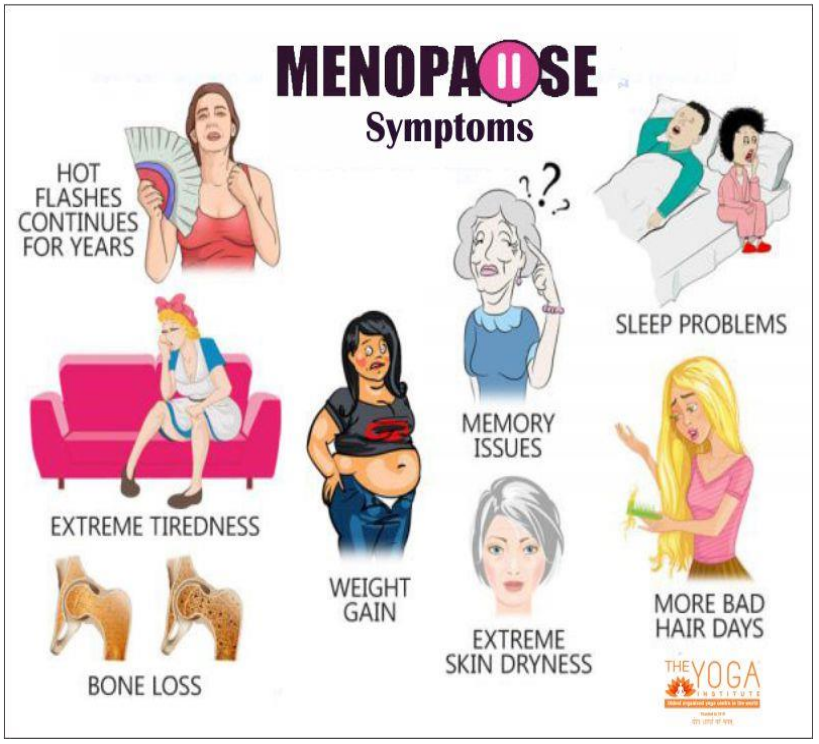
Menopause and its Symptoms:





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Brief Description of Hormone Replacement Therapy (HRT)

What is HRT?

- HRT is mainly used to relieve women from menopausal symptoms
- It has been used for more than sixty years
- HRT contains female sex hormones estrogen and/or progesterone
- First available in the United Kingdom in 1965

Routes of Administration

- Oral tablets, transdermal patches, injections, topical gels, and ointments.

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Study design and patients selection criteria

- Cases are patients of age 46 years and above who received any kind of HRT.
- Controls are matched with cases by year of birth and general practice (GP).
- Patients with all kinds of cancer, acute myocardial infarction (AMI), serious heart failure, stroke (except TIA), chronic kidney disease (CKD) stage 3-5, dementia, oophorectomy before 45, premature ovarian insufficiency, premature menopause and surgical menopause are excluded.
- Primary outcome of interest is all-cause mortality. Secondary outcomes are osteoporosis, dementia, cardiovascular disease, type II diabetes, and hormonal cancers.
- **Follow up period between 1984 to 2017**.
- **Working data consists of 112,354 cases and 245,320 matched controls**.

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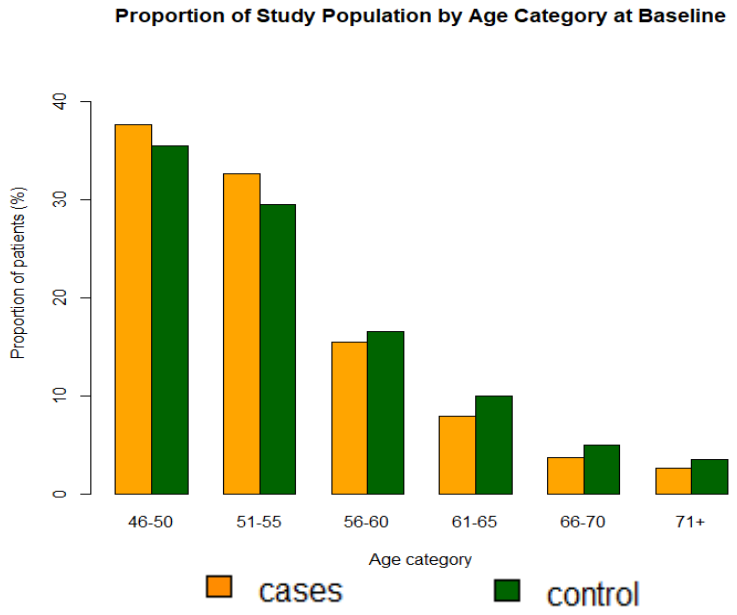
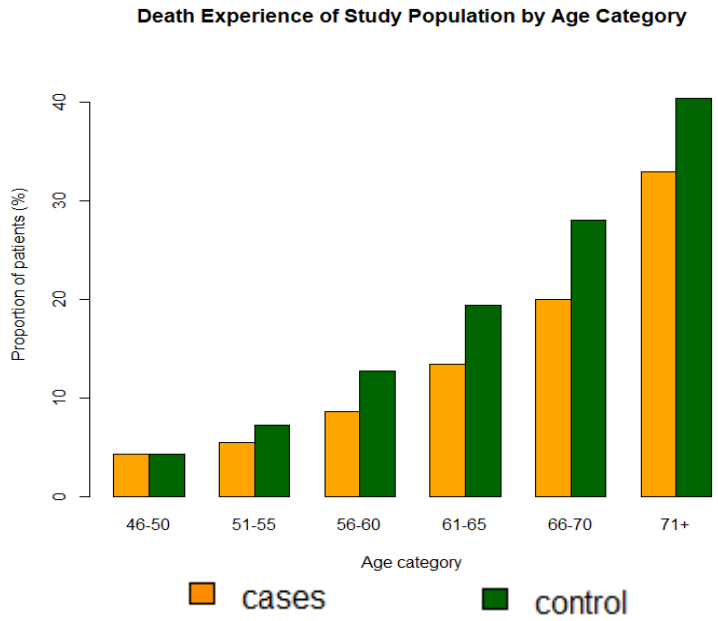
Age distribution at first HRT prescription and death experience at follow-up





Age-group	46-50	51-55	56-60	61-65	66-70	71+
Cases	42269	36680	17362	8930	4185	2928
Controls	87125	72497	40688	24382	12160	8468

Age-group	46-50	51-55	56-60	61-65	66-70	71+
Cases	1809	1985	1498	1199	837	965
Controls	3747	5260	5166	4718	3414	3423

- Majority of women started HRT between 46-55 years of age
- There are more death in controls than cases in all age category

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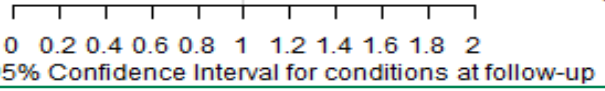
Hazard ratios and 95% confidence intervals of the conditions developed at follow up

Conditions	Age group at study entry	Hazard Ratio (95% CI)
PVD	46-50	1.21(1.18-1.25)
	51-55	1.15(1.12-1.19)
	56-60	1.17(1.13-1.22)
	61-65	1.23(1.17-1.30)
Osteoporosis	46-50	1.10(1.04-1.12)
	51-55	0.94(0.91-0.97)
	56-60	0.95(0.91-0.99)
	61-65	1.01(0.96-1.10)
Diabetes (Type II)	46-50	0.94(0.90-0.98)
	51-55	0.80(0.77-0.84)
	56-60	0.80(0.75-0.85)
	61-65	0.82(0.77-0.90)
Breast cancer	46-50	1.56(1.47-1.67)
	51-55	1.61(1.51-1.72)
	56-60	1.62(1.48-1.76)
	61-65	1.64(1.46-1.84)
Dementia	46-50	1.34(1.20-1.50)
	51-55	1.14(1.04-1.25)
	56-60	1.21(1.11-1.32)
	61-65	1.15(1.05-1.26)
Heart failure	46-50	1.11(1.00-1.22)
	51-55	0.90(0.82-0.98)
	56-60	0.81(0.73-0.89)
	61-65	0.74(0.66-0.84)
Myocardial Infarction	46-50	1.40(1.27-1.54)
	51-55	0.96(0.88-1.10)
	56-60	0.84(0.75-0.93)
	61-65	0.97(0.85-1.10)
TIA	46-50	1.47(1.32-1.64)
	51-55	1.28(1.17-1.41)
	56-60	1.23(1.11-1.36)
	61-65	1.21(1.10-1.36)



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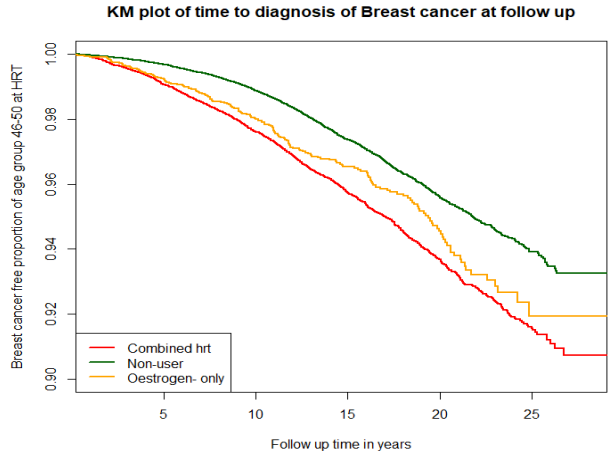
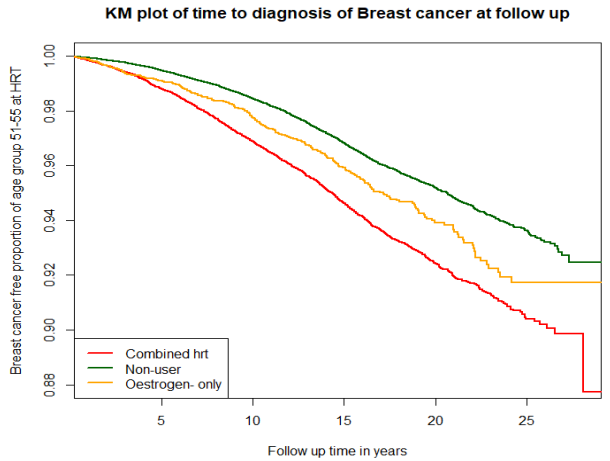
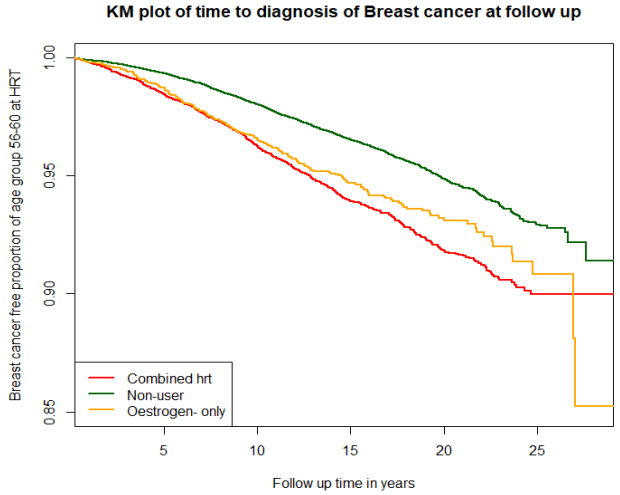
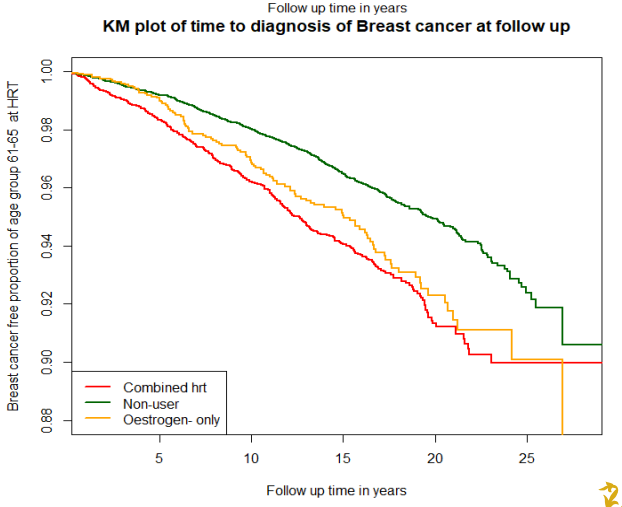
Time to diagnosis of Breast cancer at follow up by age category at HRT and its type









- In all age category HRT users developed more breast cancer than non-user at follow up

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Survival model of all-cause mortality

- The following predictors were used in the survival modelling:
  - **Socio-economic status:** Townsend score
  - **Lifestyle:** Smoking status, body mass index (BMI)
  - **Health:** Type II diabetes, hypertension, hypercholesterolaemia, peripheral vascular disease (PVD)/peripheral arterial disease (PAD), coronary heart disease (CHD), oophorectomy/hysterectomy status, systolic and diastolic blood pressure
  - **Demography:** Age category at first HRT and birth cohort
  - **Medication**: HRT (estrogen-only, estrogen and progesterone), antihypertensive drugs
- Patients with complete information for all of the above covariates has been selected for full case analysis
- Final model also included interactions of smoking with BMI and type II diabetes

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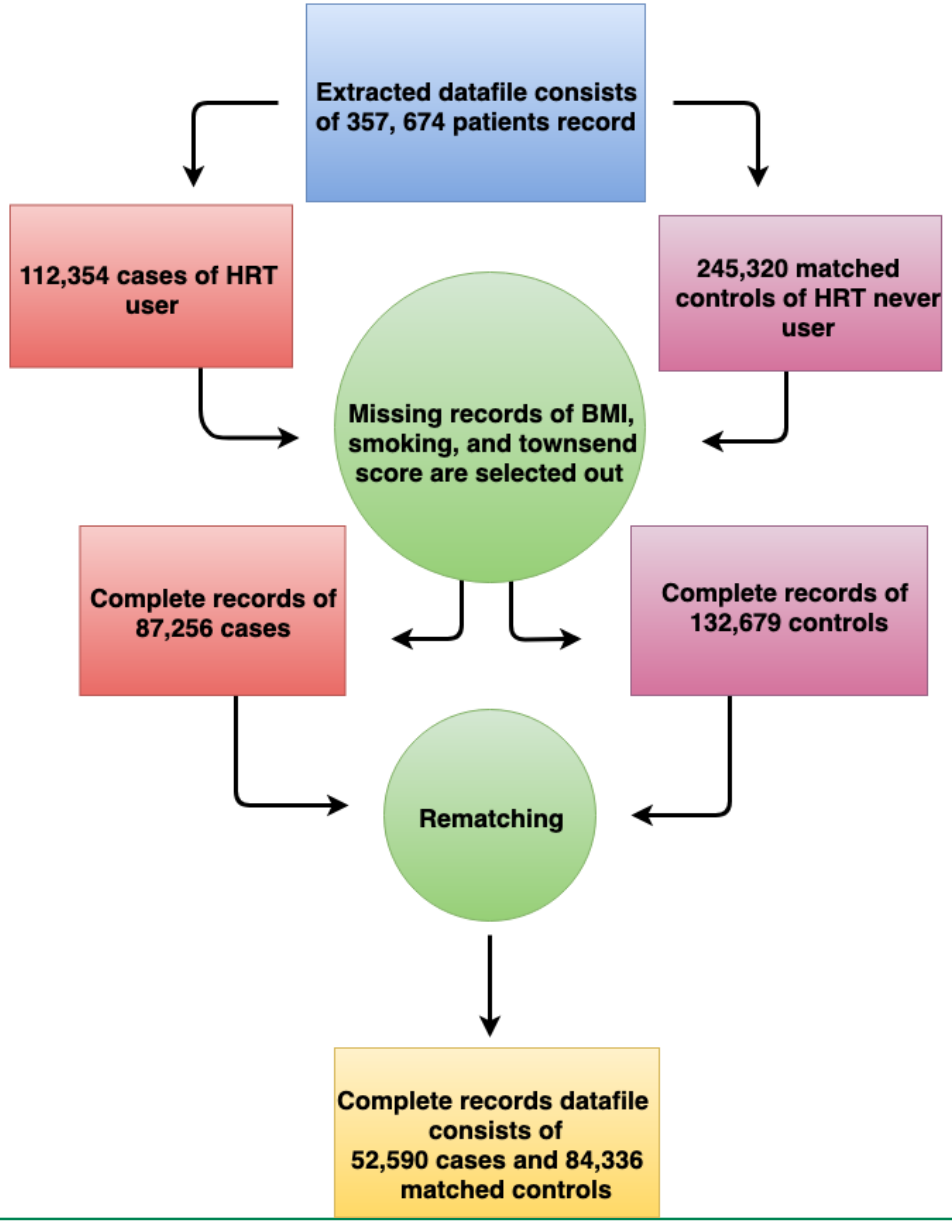
Selection of patients with complete records:



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Grambsch and Therneau test

	rho	chisq	p
hrt_cat_1Combined	-0.002697	0.074411	0.785020029057
hrt_cat_1Oestrogen-only	-0.000269	0.000753	0.978111154356
Age.cat51-55	-0.031085	10.057256	0.001517490554
Age.cat56-60	-0.027581	7.989151	0.004705847114
Age.cat61-65	-0.040494	17.268775	0.000032447539
B.cohort1931-1940	-0.026251	7.131065	0.007575972010
B.cohort1941-1950	-0.046838	22.712986	0.000001880925
B.cohort1951-1960	-0.042161	18.070751	0.000021284617
hypertension_cat_treated	-0.014381	2.178700	0.139932572339
hypertension_cat_untreated	0.012651	1.655491	0.198213197224
bmi_catObese	0.003277	0.110294	0.739809895849
bmi_catOverweight	-0.004197	0.181653	0.669956369590
smoking_cat_current	-0.051673	27.301012	0.000000174120
smoking_cat_ex	-0.023847	5.853903	0.015542544963
townsend_2	0.001919	0.038061	0.845320438510
townsend_3	-0.004281	0.188900	0.663833458455
townsend_4	-0.003795	0.148532	0.699942607104
townsend_5	-0.007716	0.615187	0.432841333884
diabetes_type2	-0.006944	0.522423	0.469809744403
osteoporosis	0.004521	0.230037	0.631496621577
CHD	-0.004256	0.188971	0.663774173883
opho.hysboth_removed	0.008301	0.719502	0.396307206913
opho.hysopho_without_hys	0.001018	0.010713	0.917564502212
bmi_catObese:smoking_cat_current	0.025841	6.906091	0.008590260141
bmi_catOverweight:smoking_cat_current	0.014928	2.301700	0.129232523293
bmi_catObese:smoking_cat_ex	0.016734	2.898047	0.088686922137
bmi_catOverweight:smoking_cat_ex	0.023806	5.863101	0.015461528170
smoking_cat_current:diabetes_type2	0.005911	0.362035	0.547378311009
smoking_cat_ex:diabetes_type2	-0.016739	2.914064	0.087810369554
GLOBAL	NA	103.604595	0.000000000257

A significant p-value(<0.05) is an indication of violation of the proportional hazard assumption in the Cox PH model

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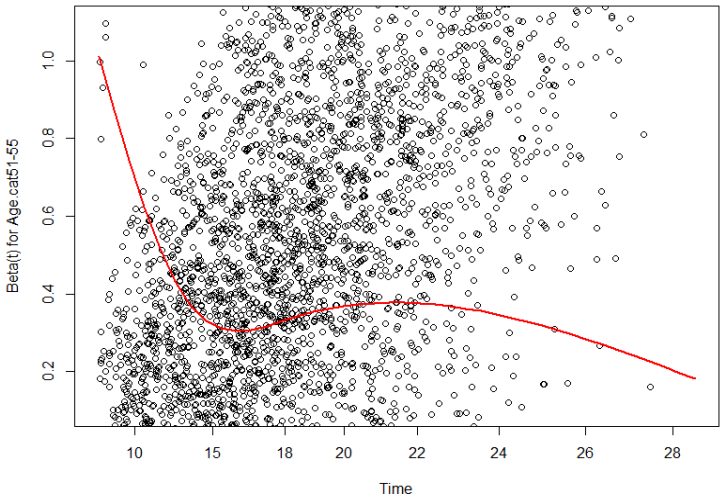
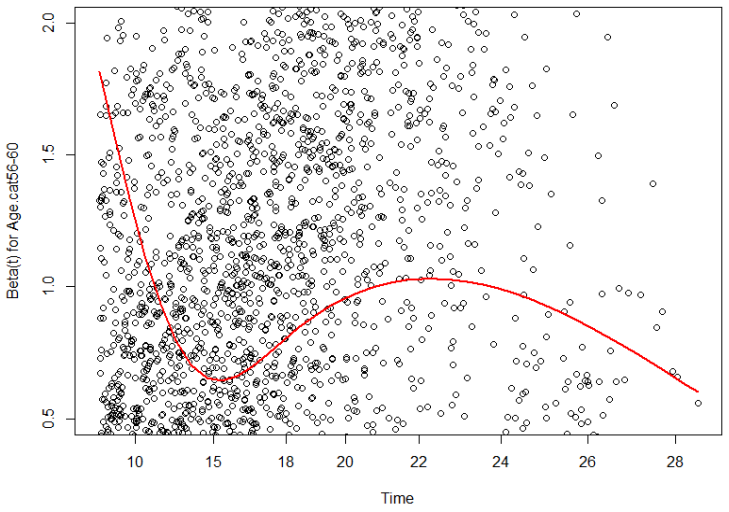
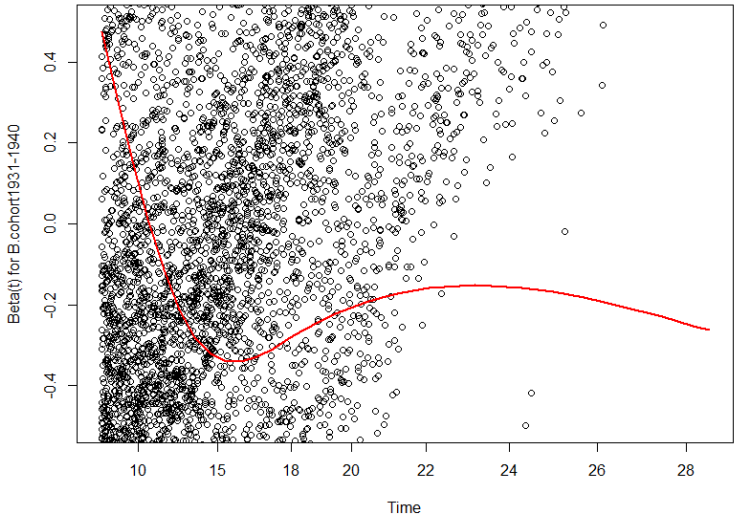
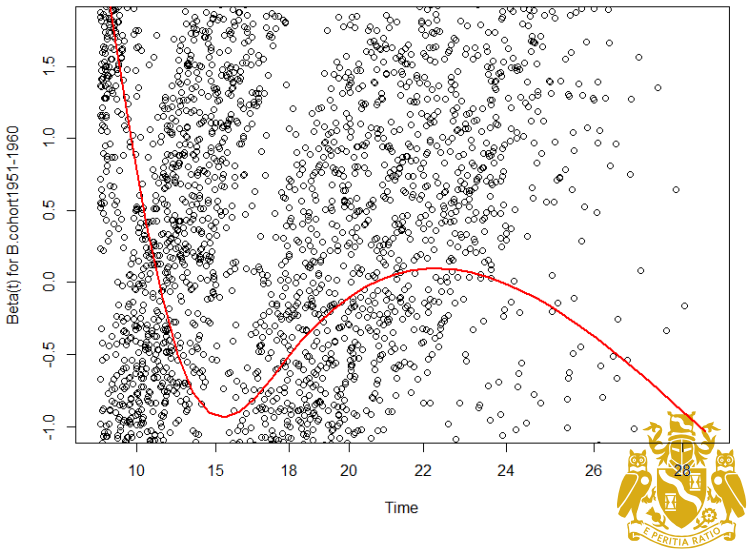
Plots of residuals:



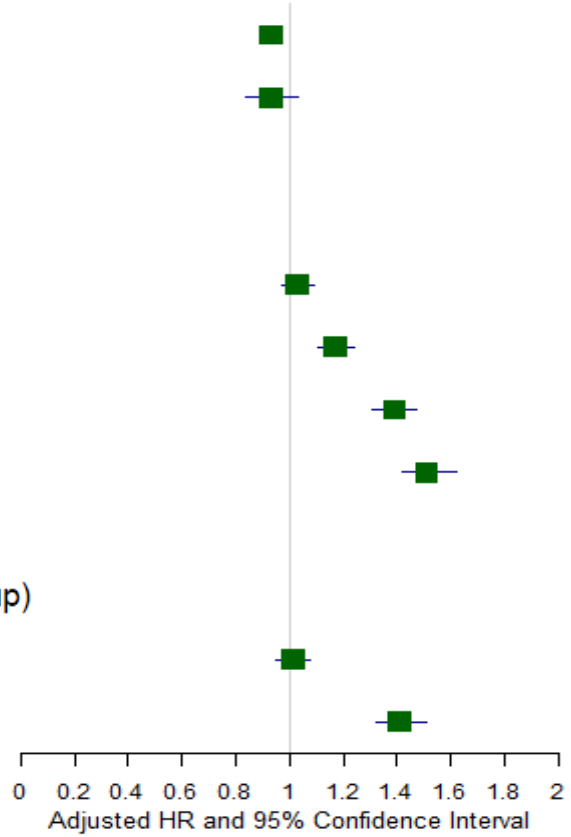






HRT model, Forest plot 1

Risk factors	Subgroups	Adjusted hazard ratio(95% CI)
HRT type	Non-user (reference group)	
	Combined HRT	0.93(0.89-0.97)
	Estrogen-only	0.93(0.84-1.03)
Townsend score	1 (reference group)	
	2	1.03(0.96-1.09)
	3	1.17(1.11-1.24)
	4	1.39(1.31-1.47)
	5	1.51(1.42-1.62)
BMI	Healthy weight (reference group)	
	Overweight	1.01(0.95-1.08)
	Obese	1.41(1.32-1.51)



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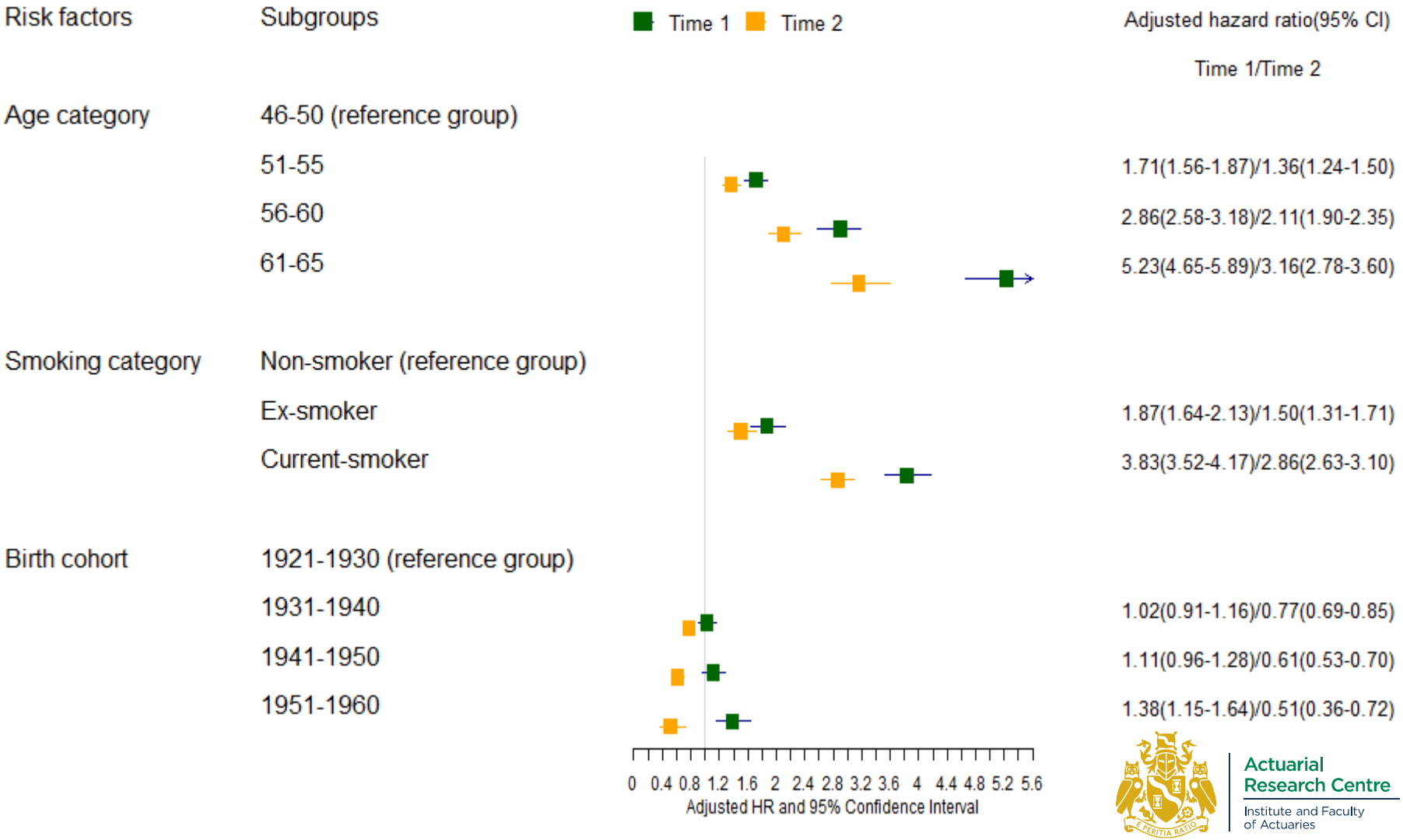
HRT model, Forest plot 2



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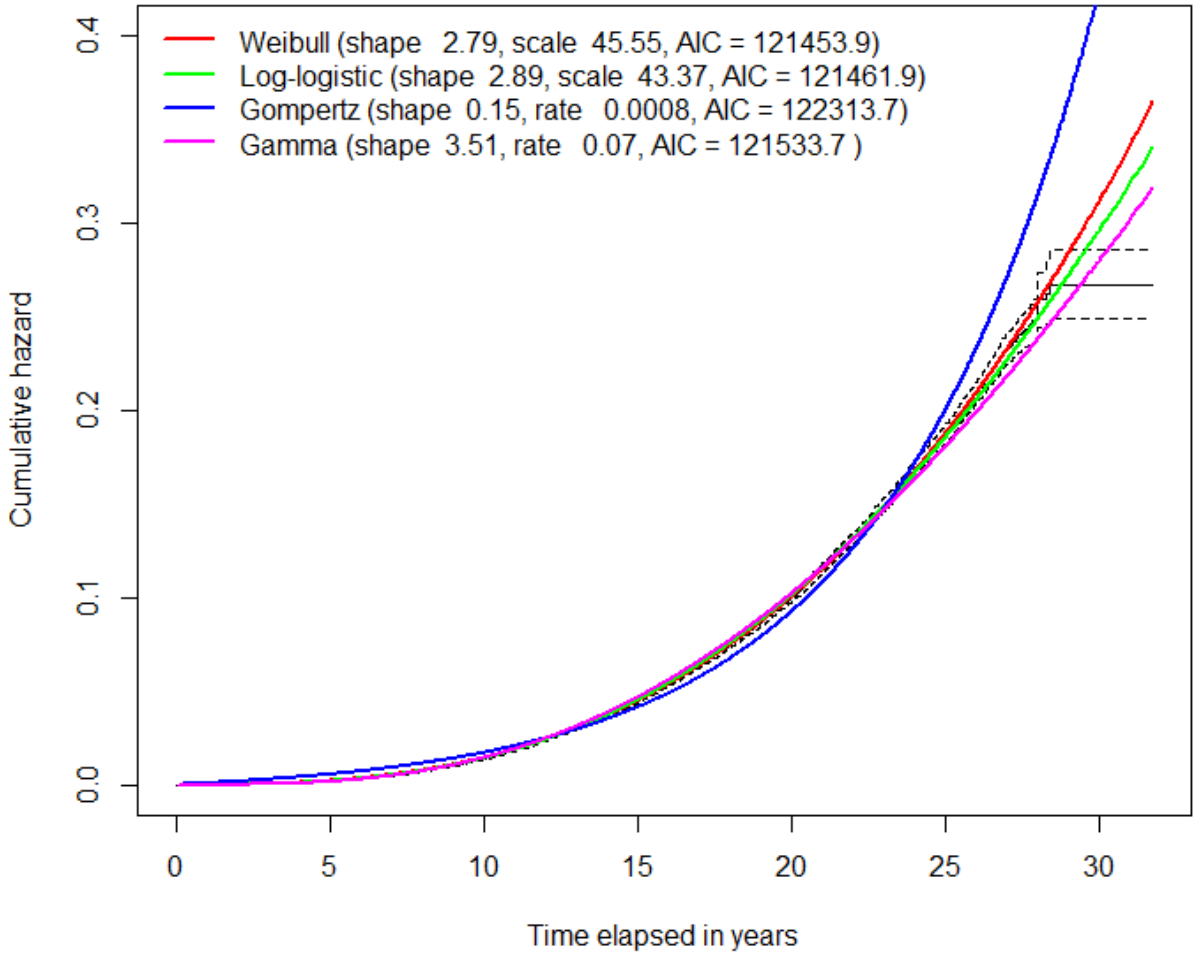
Baseline hazard function fitted with different parametric distributions:



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Future Work:

- Multiple imputation
- Models for imputed data.
- Translation of models into actuarial analysis
- Landmark analysis

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