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The effect of Hormone Replacement Therapy on the survival of UK women: a retrospective cohort study 1984-2017

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Abstract

OBJECTIVE: To estimate the effect of hormone replacement therapy (HRT) on the hazards of overall and age-specific all-cause mortality in women aged 46 to 65 at first prescription.

DESIGN AND SETTING: Retrospective matched cohort study in the United Kingdom (UK) between 1984 and January 2017 using electronic primary care records from The Health Improvement Network (THIN) database.

POPULATION: 105,199 cases of HRT users who were born between 1920 to 1960 and started treatment first time between 1984 and 2017, and 224,643 controls matched on age and general practice.

MAIN OUTCOME MEASURES: The hazards of all-cause mortality associated with HRT were estimated by a parametric Weibull-Cox regression model adjusted for age at first HRT treatment, type of HRT, year of birth, type 2 diabetes, hypertension and its treatments, coronary heart disease, oophorectomy/hysterectomy status, body mass index, smoking, and deprivation status.

RESULTS: During 32 years of follow-up, the adjusted hazard ratio of overall all-cause mortality in combined HRT users was 0.91(95%CI,0.88-0.94), and in oestrogen-only users was 0.99(0.93-1.07), respectively, compared to non-users. Age-specific adjusted hazard ratios for all-cause mortality in groups aged 46 to 50, 51 to 55, 56 to 60, and 61 to 65 years at first treatment were 0.98(0.92-1.04), 0.87(0.82-0.92), 0.88(0.82-0.93), and 0.92(0.85-0.98), in combined HRT users compared to non-users, and 1.01 (0.84-1.21), 1.03(0.89-1.18), 0.98(0.86-1.12), and 0.93(0.81-1.07) in oestrogen-only users, respectively.

CONCLUSION: Combined HRT reduced the risks of overall all-cause mortality in women aged between 46 and 65 years at first treatment. Oestrogen-only formulation was not associated with increased risk of all-cause mortality. This new information on the long-term risks and benefits of HRT should be used to inform women deciding whether to start or continue with HRT.

1 Introduction

Hormone Replacement Therapy (HRT) is considered to be an effective treatment in relieving perimenopausal symptoms caused by deficiency of female sex hormone oestrogen and progesterone [1]. Other known benefits of HRT are reduction in bone loss, cardiovascular disease, and improvement in quality of life after menopause [2; 3; 4; 5; 6]. HRT has been used for more than six decades [7]. Although it is effective in alleviating menopausal symptoms [8], incidence of adverse effects, such as an increased risk of gynaecological cancers [6; 9; 10] make long term HRT use controversial. Numerous studies of HRT have been conducted in the past, mostly focused on morbidity [2; 6; 9; 10; 11] or cause-specific mortality [6; 12; 13]. However, the actual benefits and risks of HRT are still disputed as results from the existing studies are contradictory. Due to the uncertainty about its impact, many symptomatic women are reluctant to receive HRT [7].

All-cause mortality summarises the net risks and benefits of using HRT. A recently conducted prospective cohort study based on self-reported questionnaires about HRT use in 29,243 Danish women aged 50 to 64 years found no impact of HRT on all-cause mortality [14]. An observational study in the United States consisting of 41,070 women aged 50 to 69 years found reduced risk of death in HRT users [4]. 2017 report from the pooled results of two arms of the Women's Health Initiative (WHI) randomised control trials of 27,347 women showed no association of HRT with total mortality in American postmenopausal women [15].

Previous studies collected information about the use of HRT mainly from survey questionnaires [16; 4; 5; 14; 17], and estimated the hazard of mortality after adjusting for age, demographic and/or lifestyle factors [6; 18; 14]. Clinical variables are important con-

founders that highly influence mortality, and hence adjustment of these factors in the analysis is required to obtain a true estimate. In a number of observational studies [4; 17], HRT users were younger and more disease free than the non-users, which may have introduced bias in favour of HRT users. Although distinct health outcomes were observed between combined and oestrogen-only HRT [6; 9; 10; 19], little is known about the impact of these two formulations on all-cause mortality separately. WHI [15] results may not be generalisable to population of all HRT users as they analysed only one fixed dose of oral oestrogen and progesterone. Moreover, participants of WHI trial were relatively older (mean age 63.4) with existing comorbidities [14; 20]. Age-specific information on the use of HRT and its long-term impact on all-cause mortality was not reported in previous studies [4; 5; 14; 17]. Furthermore, past studies did not provide information about handling of missing data [4; 17] and on the possibility of the time varying hazards [13; 16; 17]. In addition, the absence of matching controls may have hindered the proper assessment of benefits and risks of HRT [3; 4; 14; 17].

A matched cohort study where the controls have the same age and background as cases and have similar health characteristics with adjustment for more confounding variables and a longer follow-up offers the potential to overcome some of the limitations in previous studies. Electronic primary health care records in the UK retain a wide range of information including comorbidities, treatment history, and some socioeconomic and lifestyle factors with a lifetime follow-up. Mortality registration is also included and regularly updated in primary care data as GPs must be informed if their patient died [21]. While there has been extensive research on HRT, no published study to date has investigated all-cause mortality associated with HRT using UK primary care data.

The main aims of this study were to estimate the effect of oestrogen-only and combined HRT on the hazards of all-cause mortality in a large cohort of women broadly representative of the British population by adjusting for a wide range of important risk factors, and to analyse age-specific effects of HRT initiation on mortality.

2 Study design

A population-based matched retrospective cohort study was designed to estimate the effect of HRT on the hazards of all-cause mortality. The Health Improvement Network (THIN) database has been used to extract patients' information on various medical conditions, treatments, demographic, and socioeconomic status. THIN is representative of the UK general population in terms of demographics, and of crude prevalence of chronic medical conditions, and mortality rates when adjusted for demographics and deprivation [22]. Currently, THIN database holds longitudinal records of 17 million anonymised patients from over 770 general practices, of which 3.1 million are actively registered, covering 6% of the UK population [23; 24].

Patients who started any formulation of oral or transdermal HRT for the first time at age between 46 and 65 years were considered as cases. Controls were never users of HRT or any type of drugs containing oestrogen and/or progesterone. Controls were matched with cases in one to up-to-three ratio by birth year and general practice (GP). The study entry date for controls was the date of first HRT prescription of their matched cases. Participants were eligible for the study if at the time of first HRT treatment they had been registered as an active patient for at least one year, and their health records had been accessed at least once within the past ten years. Patients with a previous history of any

kind of cancer, acute myocardial infarction, serious heart failure, stroke (except transient ischaemic attack), chronic kidney disease (stage 3 to 5), dementia, oophorectomy before 45 years of age, premature ovarian insufficiency, premature menopause, and surgically induced menopause were excluded from the study at baseline to assess the long term impact of HRT on healthy postmenopausal women.

The analysis included patients who were born between 1920 and 1960 and started HRT at the selected age anytime from 1984 until the study end date which was 1st January 2017, and their matched controls. Participants were followed up from the date of first HRT prescription until death, or transfer to another GP practices, or study end date whichever comes first. Thus, the follow-up period was up to 32 years. Patients who were transferred to another GP during the study period were no longer followed up, and their observation time was censored at that point of time. The outcome was measured by time to the event of death from any cause from the date of first HRT prescription. Data extraction of this study was performed using the Structured Query Language (SQL) server 2016.

3 Covariates selection

The covariates selection for this study were based on literature review and expert knowledge within the team [25]. The baseline characteristics were extracted from the latest records before the study entry date, i.e., the date patients received first HRT prescription. The covariates included in the analyses were age at first HRT treatment, type of HRT, year of birth, type 2 diabetes, osteoporosis, peripheral arterial/vascular disease (PAD/PVD), coronary heart disease (CHD), hypertension and its treatments, hypercholesterelomea, oophorectomy/hysterectomy status, smoking, body mass index (BMI), and deprivation

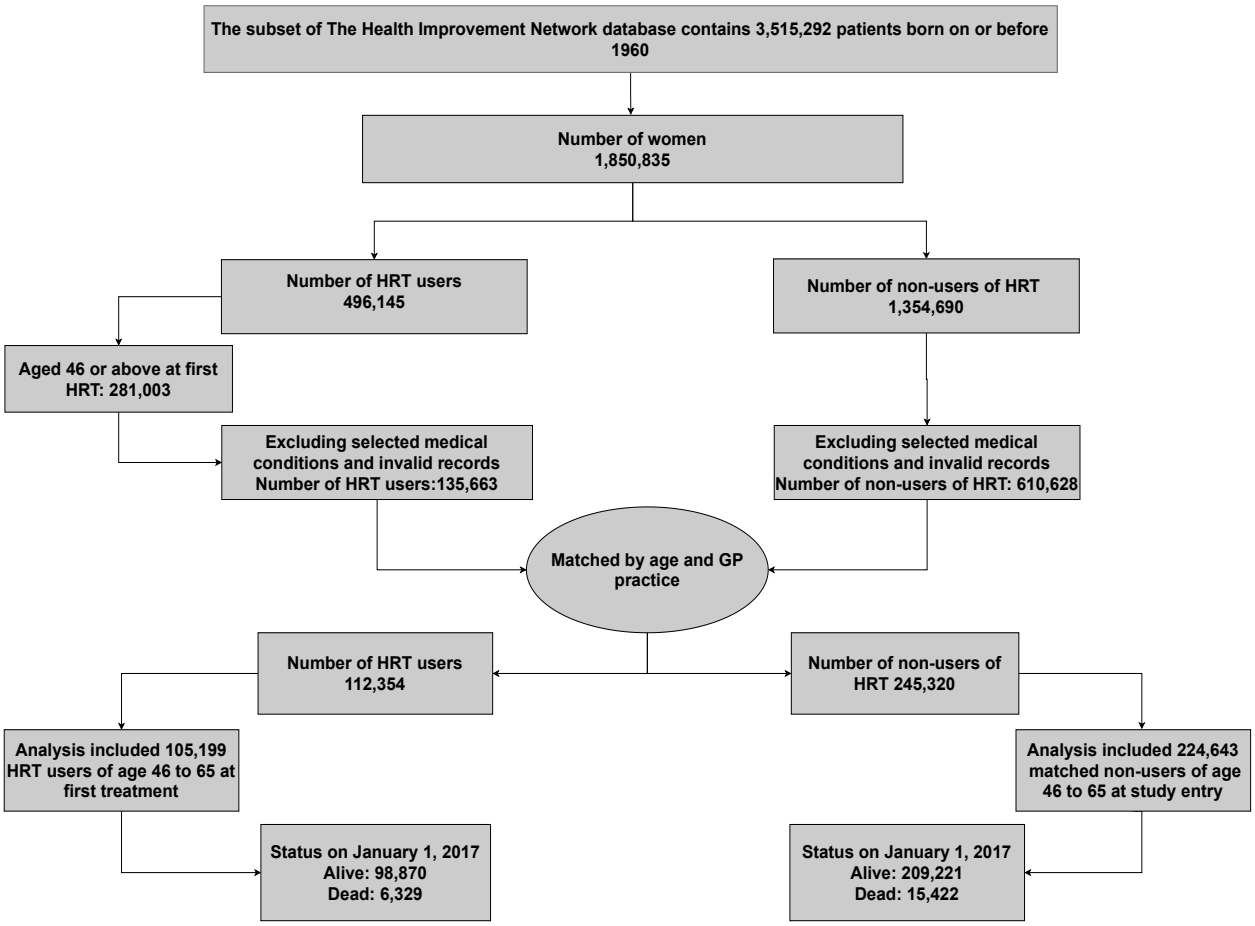

Figure 1: Selection procedure of study population.

status. Types of HRT were classified as oestrogen-only or combined formulation. Cases were identified as combined HRT users if they received oestrogen and progesterone either in a one single prescription or in two separate prescriptions. The British National Formulary (BNF) drug codes were used to select HRT type [26]. Patients with selected medical conditions were identified using the corresponding Read codes which are available online at ClinicalCodes.org [27].

Socio-economic status in THIN is coded by the Townsend quintiles index based on patients' material ownership and living condition, where the first quintile represents least deprived and the fifth represents the most deprived group [28]. In the final analysis, patients within Townsend score quintiles 1 and 2 were re-coded as low, quintile 3 as medium, quintiles 4 and 5 as high level of deprivation since there were no statistically significant differences in hazards found among patients within quintiles 1 and 2, and quintiles 4 and 5. Similarly, BMI was categorised into two levels, healthyweight/overweight and obese. To classify hypertension, measurements of systolic and diastolic blood pressure (SBP/DBP) were used in conjunction with Read codes, as previous research showed that using only Read codes to select hypertensive patients in THIN underestimates the actual prevalence of hypertension in the UK [29]. Depending on the use of anti-hypertensive drugs, hypertensive patients were categorised as treated or untreated. Uterine and ovarian status was grouped into three levels: intact (no history of removal of uterus and ovaries), hysterectomy with oophorectomy (hysterectomy and at least one ovary removed), and oophorectomy only (one or both ovaries removed). Due to a very small proportion of women with hysterectomy who have not had oophorectomy, this group was not included in the model. Year of birth variable was grouped into four decade-long birth cohorts. Information about

parity and age at menopause were not included in the analyses because of very low rates or unsystematic way of recording in THIN.

4 Statistical analyses

The hazards of all-cause mortality associated with HRT were initially estimated by fitting Cox proportional hazards regression model. The outcome variable was time from the date patient started first treatment to the date of death from any cause. The model included second order interaction effects of all variables with main exposure HRT, and also interactions of all medical conditions with the lifestyle variables. Backward elimination was applied to select the variables at 5% significance level for the main exposures, and 1% significance level for the interactions. The contribution of the covariates in explaining the variation of the hazard in the Cox regression model was assessed by ANOVA. Grambsch and Therneau's test [30] was performed to check the non-proportionality of hazards at 5% level of significance and was found to be significant. Consequently, a parametric Weibull-Cox regression model [31] was used to estimate both the shape effects of the variables with the time-variant hazards, and the scale effects. This model incorporates the Weibull baseline hazard function with Cox-regression model for estimating the scale and shape parameters. General practices were included in the model as a random effect or frailty to account for the unobserved heterogeneity of patients between practices. Four separate survival models were also fitted to assess the impact of HRT by 5-year age group at initiation on all-cause mortality. Same sets of explanatory variables were adjusted for in the full case model and in age subgroup analyses.

Multilevel multiple imputation was used to deal with missing data. Ten imputed

datasets were generated and analysed independently for full model and also for each subgroup model. The distribution of the variables in complete and imputed datasets were similar (supplementary Table 3). Rubin's rules [32] were applied to pool estimated parameters from the models on the imputed datasets. The overall performance of the models were tested by the concordance, and its values of 0.7 in full model, and 0.68−0.70 in the subgroup models indicate a good-fit [33]. All analyses were performed in statistical software R version 3.6.1 using the packages "survival", "MASS", "rms", and "ucminf". R package "jomo" was used for joint modelling multiple imputation.

5 Results

5.1 Participants characteristics and follow-up

105,199 HRT users started treatment for the first time at ages between 46 and 65 years in 1984−2017 (Table 1). There were 224,643 age and GP matched controls of HRT non-users. The mean (± standard deviation) age of women at first treatment was 53 (± 5.02) years. The mean duration of HRT use was 6.0 (SD ± 4.8) years. Among HRT users, 17,606 (17%) received oestrogen-only and 87,593 (83%) received combined therapy. Around 75% of women were prescribed first HRT at 46 to 55 years of age.

There were missing values in smoking (14%), BMI (24%), Townsend deprivation index (11%), and hypertension (28%) status. The higher proportion of missingness was among controls for smoking, BMI, and hypertension (Table S1). Incomplete medical records were more common in younger patients than the older, and in patients without any chronic medical conditions or treatments. There were more missing records in patients who were

Table 1: Selected baseline characteristics of cases and matched controls in the study populations.

Characteristic	No.(%) of patients[2]			
	Cases			**Controls**
	Estrogen-only ($n = 17606$)	Combined HRT ($n = 87593$)	Total ($n = 105199$)	($n = 224643$)
Age group at HRT				
46−50	5035 (28.6)	37219 (42.5)	42254 (40.2)	87108 (38.8)
51−55	6011 (34.1)	30654 (35.0)	36665 (34.9)	72486 (32.3)
56−60	4069 (23.1)	13286 (15.2)	17355 (16.5)	40674 (18.1)
61−65	2491 (14.1)	6434 (7.30)	8925 (8.5)	24375 (10.9)
Birth cohort				
1921−1930	573 (3.3)	1361 (1.6)	1934 (1.8)	5565 (2.5)
1931−1940	5450 (31.0)	18940 (21.6)	24390 (23.2)	55047 (24.5)
1941−1950	8438 (47.8)	44453 (50.7)	52891 (50.3)	96142 (42.8)
1951−1960	3145 (17.9)	22839 (26.1)	25984 (24.7)	67889 (30.2)
Hypertension				
No[1]	10017 (56.9)	55266 (63.1)	65283 (62.1)	134337 (59.8)
Treated[1]	4419 (25.1)	18657 (21.3)	23076 (22.0)	49421 (22.0)
Untreated[1]	3170 (18.0)	13670 (15.6)	16840 (16.0)	40885 (18.2)
Uterine/ovarian status				
Intact	6779 (38.5)	78214 (89.3)	84993 (80.8)	203625 (90.6)
Hysterectomy with oophorectomy[3]	9945 (56.5)	1067 (1.2)	11012 (10.5)	6502 (2.9)
Oophorectomy only	882 (5.0)	8312 (9.5)	9194 (8.7)	14516 (6.5)
PAD/PVD	1348 (7.7)	7498 (8.6)	8846 (8.4)	17340 (7.7)
Diabetes Type II	317 (1.8)	1233 (1.4)	1550 (1.5)	5089 (2.3)
CHD	336 (1.9)	1033 (1.2)	1369 (1.3)	3130 (1.4)
Osteoporosis	352 (2.0)	2101 (2.4)	2453 (2.3)	4215 (1.9)
Hypercholesterolaemia	254 (1.4)	972 (1.1)	1226 (1.2)	2605 (1.2)
Body mass index				
Healthy weight/overweight[1]	13109 (74.5)	69023 (78.8)	82132 (78.1)	161294 (71.8)
Obese[1]	4497 (25.5)	18570 (21.2)	23067 (21.9)	63349 (28.2)
Smoking status				
Non[1]	10966 (62.3)	50716 (57.9)	61682 (58.6)	141301 (62.9)
Ex[1]	3187 (18.1)	15854 (18.1)	19041 (18.1)	35269 (15.7)
Current[1]	3468 (19.7)	21022 (24.0)	24490 (23.3)	48298 (21.5)
Deprivation status				
Low[1]	9648 (54.8)	47738 (54.5)	57386 (54.5)	117488 (52.3)
Medium[1]	3662 (20.8)	17957 (20.5)	21616(20.5)	46950 (20.9)
High[1]	4296 (24.4)	21811 (24.9)	26107 (24.8)	60204 (26.8)

[1]The reported prevalence of variables with missing values are the mean of ten imputed datasets. Due to missingness in systolic and diastolic blood pressure, missing values were generated in hypertension category.
[2]All values are reported as No. (%)
[3]Hysterectomy and at least one ovary removed

born in earlier birth cohorts. This agrees with the previous research that reported that recording has greatly improved after the initiation of the Quality and Outcomes Framework (QoF) in 2004 [34]. The prevalence of selected medical conditions was nearly the same in HRT users and non-users at baseline for most conditions (Table 1). However, HRT users underwent more oophorectomy and hysterectomy than the non-users, and there were more osteoporotic patients among first HRT starters in older age group at baseline (Table S3). It is known that these conditions are more prevalent among HRT users as these are often the cause of prescribing HRT treatments [8]. There were more obese (BMI$\geq$30 kg/m^2) women in controls, whereas more healthy weight/overweight women in cases. The proportions of ex-smokers and current smokers were slightly higher in HRT users. More than half of the study population lived in low deprivation level areas. In earlier birth cohorts more women took oestrogen-only HRT, and in later birth cohorts more women took combined HRT (Table 1).

The average follow-up of women was 13.5 ($\pm$) years. During follow-up, 21,751 women died in total. There were 6,329 (6%) deaths in cases, and 15,422 (7%) in controls. Among cases, 1,110 (6.3%) deaths were in oestrogen-only users, and 5,219 (6%) in combined HRT users.

5.2 Results of survival modelling of HRT

The significant covariates included in the final model were age at HRT, birth cohort, type of HRT, hypertension and its treatment, coronary heart disease (CHD), type 2 diabetes, oophorectomy/hysterectomy status, body mass index (BMI), smoking, and deprivation status. All significant variables in the full model were also significant in age subgroup

models. There was a significant interaction of BMI with smoking in all models and an extra interaction of smoking with type 2 diabetes found in full model. There was no significant interaction of HRT with other variables; which means that the survival effect of HRT on the hazards of all-cause mortality were the same across different subgroups, such as smoker and non-smoker. The unadjusted and adjusted effects of HRT on the hazards of all-cause mortality for the full data and for the four age subgroup models are presented in Figure 2.

The adjusted hazard ratios of all-cause mortality associated with HRT were time-invariant during follow up. Overall, the hazard of death was lower in combined HRT users compared to non-users. Combined HRT reduced the hazard of all-cause mortality by 9% (HR, 0.91; 95% CI, 0.88 - 0.94) in women of age between 46 and 65 years at first HRT treatment compared to the non-users at the same age. When analysed by age subgroups, it was found that combined HRT reduced the hazards of all-cause mortality by 13%, 12%, and 8% in women who received first treatment at age 51 to 55 (0.87; 0.82 - 0.92), 56 to 60 (0.88; 0.82 - 0.93), and 61 to 65 (0.92; 0.85 - 0.98), respectively. The effect of combined HRT was not statistically significant in 46 to 50 (0.98; 0.92 - 1.04) age group at first treatment. There was no association of oestrogen-only HRT with women's survival in the full model (HR 0.99; 95% CI, 0.96 - 1.22) as well as in subgroups (Figure 2).

Oophorectomy and hysterectomy were associated with improved survival prospects in women, in which the reduction in the hazards of all-cause mortality was highest in the oldest age cohort and lowest in the youngest age cohort at first HRT treatment (Figure 5 in the supplementary materials). In the full model, the hazard was reduced by 24% (0.76; 0.71 - 0.81), and in the subgroup analyses, the hazard reductions ranged from 28% (0.72;

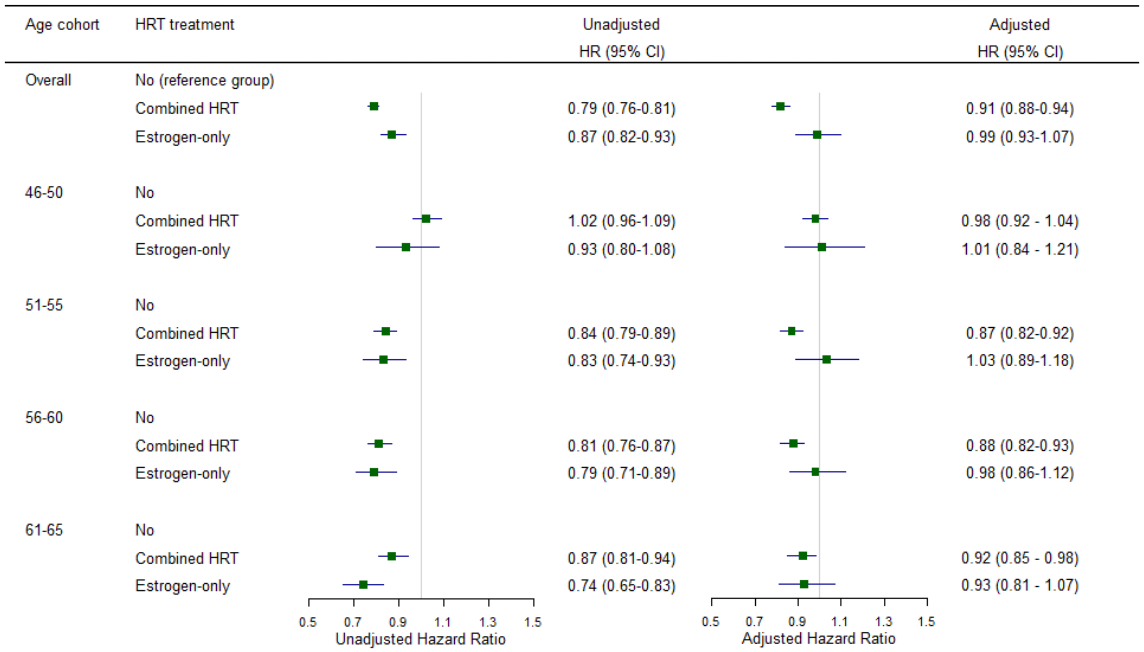

Figure 2: Unadjusted and adjusted hazard ratios of all-cause mortality associated with the use of HRT by age at first treatment. The age categories included patients who started HRT at that age and all of their matched controls. The hazard ratios (95% confidence intervals) were adjusted for age at first HRT, birth cohorts, type of HRT, oophorectomy/hysterectomy status, type 2 diabetes, coronary heart disease, hypertension and its treatments, deprivation status, body mass index, and smoking status. General practice was also included in the model as a frailty.

0.64 - 0.82) in the oldest age cohort to 19% (0.81; 0.65 - 0.99) in the youngest age cohort for women whose ovaries and uterus are removed compared to the intact group.

Both treated and untreated hypertension increased the hazards of all-cause mortality. In the full data, the hazard ratios of the treated and untreated hypertension were 1.51 (95% CI, 1.43 - 1.59), and 1.31 (1.24 - 1.38), respectively, compared to women with no hypertension. These findings did not differ much in the age subgroup models (Figure S1).

There were significant survival variations by women's deprivation status. The hazards of all-cause death was greatest to the high level of deprivation, and also greater at medium level of deprivation compared to the low deprivation. Overall, women living at high level of deprivation areas faced 42% increased hazards of death (1.42; 1.38 - 1.47) than the women at low deprivation areas. In the subgroup analyses, the hazard ratios of all-cause mortality at high deprivation was greatest in the youngest (46 to 50) age cohort (1.53; 1.42 - 1.64) and lowest in the oldest age (60 to 65) cohort (1.30; 1.20 - 1.36). In addition, interaction of BMI and smoking had considerable impact on women's survival. The hazard ratios of all-cause mortality in current smokers compared to non-smokers were higher in healthy weight/overweight women than in obese women in all age cohorts. In ex-smokers compared to non smokers, the risk was higher in obese women than in the healthy weight/overweight patients.

As the hazards of all-cause mortality by birth cohort were not time-invariant, both shape and scale parameters were estimated for this risk factor. In Figure 3, the hazards of all-cause mortality for four age subgroups at first HRT initiation by HRT type are plotted for women born in four different birth cohorts. In all birth cohorts, the combined HRT users had reduced hazards of mortality, and oestrogen-only HRT users had increased

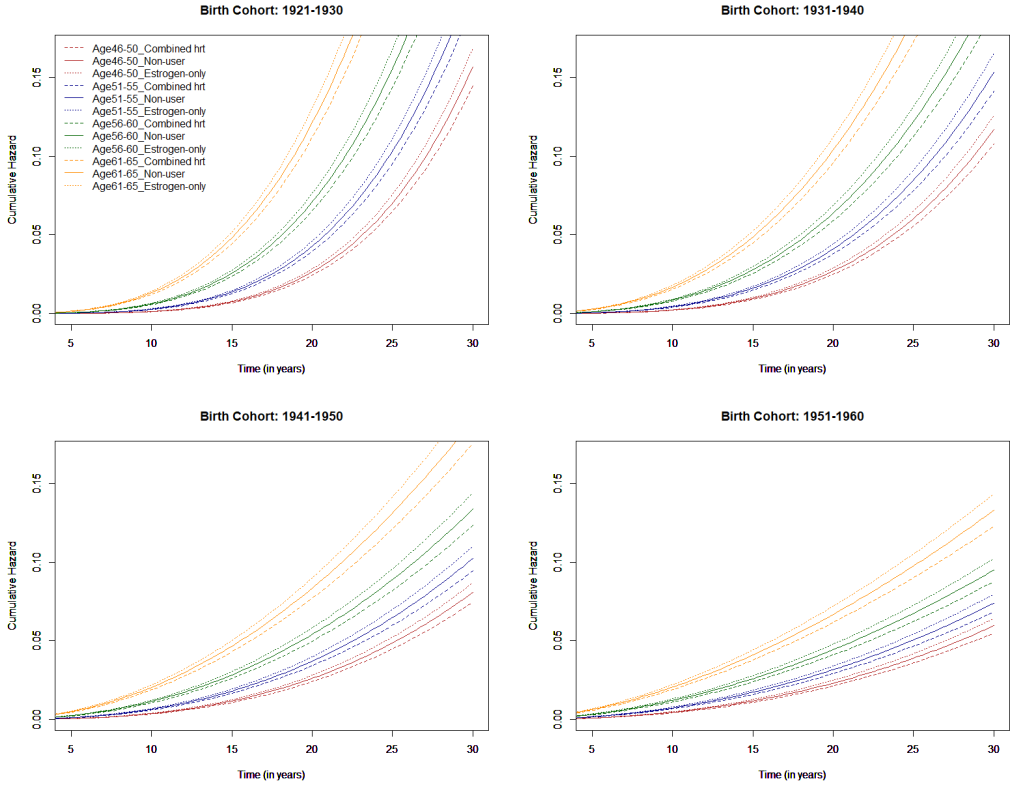

Figure 3: Cumulative hazard plots of all-cause mortality for four age subgroups of 46 to 50, 51 to 55, 56 to 60, and 61 to 65, respectively at first HRT treatment by HRT type in four birth cohorts.

hazards of mortality in comparison with the non-users. However, the adjusted effect of oestrogen-only HRT was not statistically significant in the full model. Comparing the hazards in the four birth cohorts, it was found that longevity increased in women born in the later birth cohorts than women who took HRT at the same age and of same type but born in the earlier cohorts.

Survival prospects also significantly varied by general practices. The variance of the frailty in the adjusted full model was 0.16 (0.14 - 0.19), and it ranges from 0.11 to 0.14 in the subgroups.

6 Morbidity analysis at follow-up

We analysed the time to diagnosis of a number of selected chronic medical conditions women developed after starting hormone replacement therapy. Kaplan-Meier survival analysis techniques were used to estimate the probabilities of diagnosis of a disease over time. The prevalence of various medical conditions that the study population developed at follow-up is shown in Table 2, and the Kaplan-Meier survival curves of a number of selected medical conditions are shown in Figure 4.

The prevalence of hypertension was the highest at follow-up for both cases and controls. The second highest prevalent condition was PAD/PVD in both groups. The diagnosis of osteoporosis was the next most common condition in cases and controls. At follow-up, HRT users had relatively more oophorectomies and hysterectomies than the non-users. The prevalence of most chronic medical conditions was found slightly higher in cases than in the controls. However, it should be taken into account that there were more missing records in controls than in the cases (Table 3). This higher proportion of diagnosis of the selected medical conditions at follow-up in HRT users could be because the cases visit the GP more frequently than the controls, and hence their health status was checked and updated more often than for the non-users of HRT.

Figure 4 presents the non-parametric estimates of time-to diagnosis probabilities of six different chronic medical conditions that the study population developed at follow-

Table 2: Prevalence of selected medical conditions women developed at follow-up by case/control status.

Medical conditions	No.(%) of patients[a]			
	Cases		**Controls**	
	Oestrogen-only ($n = 17606$)	Combined HRT ($n = 87593$)	($n = 224643$)	P-value[b]
Hypertension	4893 (48.8)	21701 (39.3)	50866 (37.8)	2.2e-16
PVD/PAD[c]	3912 (24.1)	19041 (23.8)	39931 (19.3)	2.2e-16
Osteoporosis	2605 (15.1)	12102 (14.2)	30396 (13.8)	8.3e-06
CKD[d]	1957 (11.1)	7649 (8.7)	19665 (8.8)	2.2e-16
Diabetes Type II	1454 (8.4)	5739 (6.7)	17030 (7.8)	2.2e-16
Hypercholesterolaemia	1418 (8.2)	6491 (7.5)	13563 (6.1)	2.2e-16
CHD[e]	1227 (7.1)	4582 (5.3)	10327 (4.7)	2.2e-16
Breast cancer	723 (4.1)	4172 (4.7)	6243 (2.8)	2.2e-16
Oophorectomy	890 (16.7)	18146 (23.4)	23812 (12.0)	2.2e-16
Hysterectomy	586 (9.3)	6893 (8.0)	8308 (3.8)	2.2e-16
Dementia	516 (2.9)	2222 (2.5)	5042 (2.3)	1.8e-11
Heart failure	433 (2.4)	1714 (2.0)	5100 (2.3)	3.2e-08
Myocardial infraction	390 (2.2)	1803 (2.1)	4427 (2.0)	4.0e-02
TIA[f]	459 (2.6)	1876 (2.1)	3860 (1.7)	2.2e-16

[a] All values are reported as No. (%), percentages were calculated by the number of conditions patients developed at follow-up over the number of patients who did not have that condition at baseline.
[b] P-values are obtained from a χ^2- test.
[c] Peripheral vascular/arterial disease [d] Chronic kidney disease [e] Coronary heart disease
[f] Transient ischaemic attack

up. The Kaplan-Meier curves show that, the combined HRT users developed less Type II diabetes than both non-users and oestrogen-only HRT users at all time points over the entire follow-up period. Until 10 years of follow-up, there were no differences in heart failure prevalence among the groups. However, after 10 years, both oestrogen only HRT users and non-users developed more heart failure. Both combined HRT and oestrogen-only HRT users developed more breast cancer than the non-users, and the proportion is slightly higher in the combined HRT group. There were lower probabilities of osteoporosis diagnosis among the combined HRT users group than the oestrogen-only and non-users after 10 years of follow-up. Oestrogen-only HRT users developed more CHD. There were no difference in the probabilities of dementia diagnosis among all group up-to 18 years of follow-up. After 18 years, oestrogen-only HRT users developed slightly more dementia.

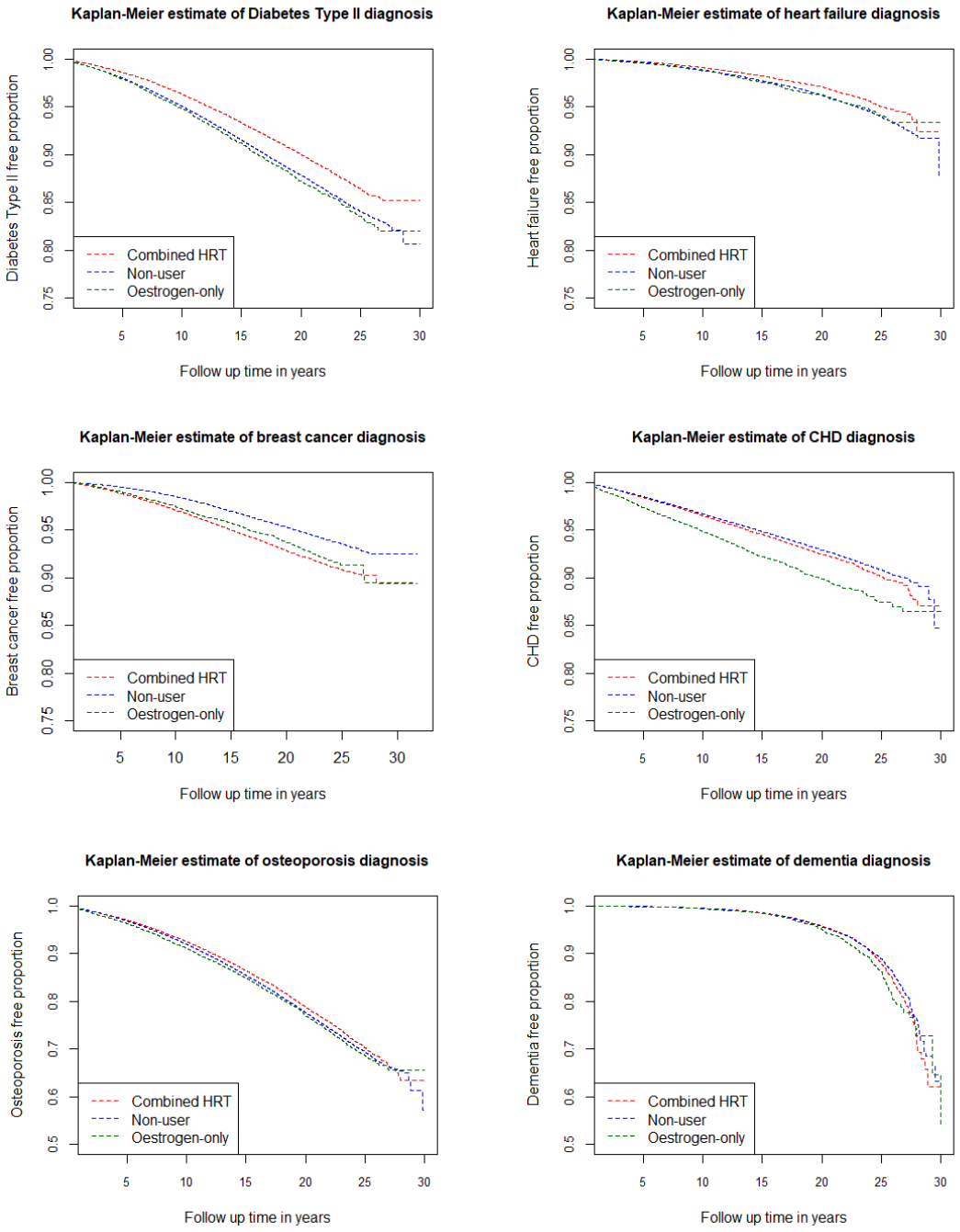

Figure 4: Kaplan-Meier survival estimates of three different groups of patients by medical conditions that were diagnosed after starting hormone replacement therapy.

7 Discussion

We assessed the effect of hormone replacement therapy on the hazards of all-cause mortality of 105,199 women aged 46 to 65 years at first prescription with 224,643 matched controls using electronically recorded data from UK primary care. Important medical, lifestyle, and socio-demographic factors were adjusted for. This large population based, retrospective cohort study found that during 13.5 years of mean follow-up, oestrogen-only HRT was not associated with significantly increased or decreased hazards of all-cause mortality (HR,0.99; 95%CI, 0.93-1.07) and combined formulation reduced the risk (HR,0.91; 95%CI,0.88-0.94).

Oestrogen-only and combined HRT were analysed separately in only a few previous all-cause mortality studies [15; 35]. Our results agree in respect to oestrogen-only HRT effects with Manson *et al.* (2017)[15] report from WHI study that found no association of oestrogen-only or combined HRT with overall mortality in women of age between 50 to 79 years [15]. However, there were some key differences between WHI and this study. WHI was a randomized control trial consisting of 13,816 postmenopausal HRT users (combined: 8506, oestrogen-only: 5310) vs placebo. The mean age of women at first treatment in the WHI study was 63.4 (SD $\pm$ 7.2) years, which is more than a decade away from menopausal transition age. WHI investigated only one single dose of oral HRT without adjustment for any potential confounders; in contrast, this study participants took various doses and preparations of oral and transdermal HRT, and the models adjusted for a wide range of important risk factors. Pooled analysis of 26,708 women from 30 trials by Salpeter *et al.* (2009) [36] showed that HRT reduced mortality by 23% in women of mean age 54 years at initiation. Our results on combined HRT agrees with Hunt *et al.* (1987)[16], Salpeter

et al. (2009)[36], Mikkola *et al.* (2015) [37], and Boardman *et al.* (2015)[38] studies which also found reduced risk of death from all cause with a variation from 27% to 58% in HRT users. However, this study found lower reduction of hazards of death than the above mentioned studies. Several factors may have caused the difference. Firstly, this study estimated hazards using a big health data from primary care while most other studies used survey or register data comprising a small number of participants. Secondly, we analysed combined and oestrogen-only HRT separately, while most other studies did not. Other possible causes of lower reduction of hazards in this study in comparison to others is that the majority of observational studies did not use matched controls, and some of them were criticised for a possibility of healthy users selection bias [17]. In this study, both cases and matched controls have the same age and similar health characteristics at baseline. In addition, this study estimated hazards of mortality by adjusting for a wide range of important confounders while most other studies adjusted for demographical and/or lifestyle variables only. However, in unadjusted analysis, we found statistically significant reduced hazards of all-cause mortality in both oestrogen-only (0.87, 0.82-0.93) and combined HRT (0.79, 0.76-0.81) users, and this reduction is greater in the unadjusted model than in the adjusted model. Our unadjusted analyses shows hazards reduction similar to that reported in Henderson *et al.* (1994)[39], Salpeter *et al.* (2009) [36], and Boardman *et al.* (2015)[38].

This study found no significant interactions of HRT type or age at initiation with other morbidities or lifestyle factors such as hypertension or smoking, which means that the effect of HRT on the hazards of all-cause mortality were the same across different patient subgroups. We found overall longevity improvement in the younger birth cohorts, but

once more, the survival benefits of HRT were independent of this trend. This study found that a history of both oophorectomy and hysterectomy was associated with a significantly improved survival prospect in women. In addition, our study agrees with the findings of Drever *et al*. [40] in respect to significant survival variation in the UK due to deprivation level. Finally, this study found significant heterogeneity in patients' survival between general practices.

Current NICE guidelines [41] recommend to offer symptomatic women combined HRT if they are not hysterectomised, or otherwise oestrogen only HRT after discussing the probable benefits and risks. According to the NICE guidelines, benefits of HRT include prevention of osteoporotic fractures, colorectal cancer, and cardiovascular disease if the therapy starts before the age of 60 years, and the risks include slight increase of coronary heart disease, storke, and thromboembolic events. All-cause mortality studies were not reviewed by NICE yet. In this study, combined HRT users had lower incidence of type 2 diabetes, heart failure, and somewhat less osteoporosis. Oestrogen only users developed more CHD events and somewhat more type 2 diabetes compared to the non-users during follow-up. Although current NICE guideline state that oestrogen only HRT is associated with little or no change in the risk of breast cancer and combined HRT can be associated with increased risk of breast cancer, we observed the increased incidence of breast cancer for both types of HRT. However, this did not translate into increased mortality in HRT users. This may be due to the higher likelihood of death from cardiovascular disease, osteoporosis and dementia than breast cancer [42]. It is, therefore, important to disseminate a balanced information on the potential benefits and risks of HRT and not to overestimate the possible risks, to allow women and their GPs to make an informed choice.

8 Strengths and limitations

This study made use of electronic primary care records which are broadly representative of the UK general population [22]. Availability of the information about all prescribed medications in primary care records enabled us to select a large number of anonymised HRT users. The matched cohort study design and exclusion of the selected medical conditions from both cases and controls cohorts allowed us to estimate the effect of HRT on the survival of healthy users compared with healthy non-users. The use of multiple imputation techniques for missing records allowed us to include nearly all extracted patients in the analyses. Use of parametric Weibull-Cox model enabled us to incorporate the time-variant covariates and to estimate their effects. A wide range of availability of information including comorbidities, treatments history, lifestyle factors and demographics in primary care records allowed us to adjust for a high number of important confounders and the interaction between them. Furthermore, this study had a long-term mean follow-up of 13.5 ($\pm$ 7.0) years.

The participants of this study received a wide variety of HRT preparations and doses, and thus these were not differentiated in the analyses. Although many important risk factors were adjusted for, there is likely to remain residual confounding by a number of other risk factors, such as age at menopause, parity, diet, and physical activity. These covariates were not adjusted for in the model due to very low proportions or unsystematic way of recording in the database. Although the covariates with incomplete records were handled by multiple imputations, which is a widely accepted method to deal with missing data, the possibility of bias remains. In addition, although THIN is broadly representative of the UK general population, due to high geographical clustering in THIN [43], further

research may needed to validate the results using data from other regions. Further research is required to explain the reasons for non-significant effect of combined HRT in 46 to 50 age group at first treatment on all-cause mortality.

9 Recommendations

These findings that oestrogen-only HRT has no impact on all-cause mortality and combined HRT reduces the overall risk offer new information for women and their doctors when they are deciding whether to start or continue HRT, and suggest that for most women the benefits of long term HRT outweigh the harms.

10 Supplementary Material

The following supplementary information can be found after the end of reference list.

Table S1. Proportion (%) of missingness in the covariates among cases and controls in full data.

Table S2. Distribution of the covariates with missing values in the complete data and imputed data.

Table S3. Baseline characteristics of the study population by age subgroups at HRT initiation in the selected covariates.

Figure S1. Adjusted effects of hysterectomy/oophorectomy status, hypertension and its treatments, and deprivation status.

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Table S1: Proportion (%) of missingness in the covariates among cases and controls in full data

	Cases			**Controls**	**Total**
Covariates	Oestrogen-only (17606)	Combined (87593)	Total (105199)	(224643)	(329842)
BMI	3356(19.1)	14016(16.0)	17372(16.5)	62629(27.8)	80001(24.3)
Smoking	2111(12.0)	7422(8.5)	9533(9.1)	37909(16.9)	47442(14.4)
Townsend	1828(10.4)	9093(10.3)	10921(10.4)	26604(11.8)	37525(11.4)
Hypertension[1]	4629(26.3)	18463(21.1)	23092(22.0)	71201 (31.7)	94293(28.6)

[1]Missing values were generated in hypertension due to missingness in SBP (29%) and DBP (31%) records.

Table S2: Distribution[1] of the covariates with missing values in the complete data and imputed data.

Covariates	Complete data[2] (108255)			Imputed data[3] (329842)		
	Oestrogen-only (6539)	Combined (36296)	Non-users (65420)	Oestrogen-only (17606)	Combined (87593)	Non-users (224643)
Hypertension						
No	3523(53.9)	22552(62.1)	37904(57.9)	10021(56.9)	55267(63.1)	134276(59.8)
Treated	1785(27.3)	8031(22.1)	15182(23.2)	4416(25.1)	18658(21.3)	49329(22.0)
Untreated	1231(18.8)	5713(15.7)	12334(18.9)	3169(18.0)	13668(15.6)	41038(18.3)
Deprivation						
Low	3646(55.8)	20001(55.1)	35326(54.0)	9648(54.8)	52057(54.5)	127761(52.3)
Medium	1327(20.3)	7388(20.4)	13457(20.6)	3662(20.8)	19574(20.5)	51088(20.9)
High	1566(23.9)	8907(24.5)	16637(25.4)	4078(24.4)	23811(24.9)	65596(26.8)
Smoking						
Non	4150(63.5)	21058(58.0)	41858(64.0)	10968(62.3)	55378(57.9)	152996(62.9)
Ex	1218(18.6)	6892(19.0)	10714(16.4)	3186(18.1)	17317(18.1)	38079(15.7)
Current	1171(17.9)	8346(23.0)	12848(19.6)	3468(19.7)	22914(24.0)	52240(21.5)
Body mass index						
Healthy weight/overweight	4734(72.4)	28371(78.2)	46299(70.8)	14170 (74.5)	74740(78.8)	172613 (71.8)
Obese	1805(27.6)	7925(21.8)	19121(29.2)	4840 (25.5)	20067(21.2)	67826(28.2)

[1]Values are reported as number (%)

[2]Patients with the complete records only

[3]Full dataset with the imputed values for missing records. The reported prevalence are the mean of ten imputed datasets.

Table S3: Baseline characteristics of the study population by age subgroups at HRT initiation in the selected covariates.

Characteristics	46-50			51-55			56-60			61-65		
	Oestrogen-only	Combined	Non-users	Oestrogen-only	Combined	Non-users	Oestrogen-only	Combined	Non-users	Oestrogen-only	Combined	Non-users
Hypertension												
No	3399(67.5)	25831(69.4)	60144(69.1)	3531(58.7)	19144(62.5)	43364(59.8)	2060(50.6)	7257(54.6)	20212(49.7)	1079(43.3)	2993(46.5)	10530(43.2)
Treated	932(18.5)	6804(18.3)	14539(16.7)	1387(23.1)	6539(21.3)	15592(21.5)	1208(29.7)	3411(25.7)	11052(27.2)	855(34.3)	1998(31.1)	8055(33.1)
Untreated	704(14.0)	4584(12.3)	12425(14.3)	1093(18.2)	4971(16.2)	13530(18.7)	801(19.7)	2618(19.7)	9410(23.1)	557(22.4)	1443(22.4)	5790(23.8)
Uterine/ovarian status												
Intact	2231(44.3)	34623(93.0)	83158(95.5)	2233(37.2)	27112(88.5)	65141(89.9)	1412(34.7)	11165(84.0)	34928(85.9)	903(36.3)	5314(82.6)	20398(83.7)
Hysterectomy with oophorectomy	2579(51.2)	286(0.8)	870(1.0)	3451(57.4)	359(1.2)	2119(3.0)	2460(60.5)	254(2.0)	1974(4.9)	1455(58.4)	168(2.6)	1539(6.3)
Oophorectomy only	225(4.5)	2310(6.2)	3080(3.5)	327(5.4)	3183(10.4)	5226(7.2)	197(4.8)	1867(14.1)	3772(9.3)	133(5.3)	952(14.8)	2438(10.0)
PAD/PVD	317(6.3)	2270(6.1)	5139(5.9)	390 (6.7)	1992 (6.5)	4494(6.2)	317 (7.8)	1009(7.6)	2969(7.3)	241(9.7)	611(9.5)	2242(9.2)
Diabetes Type II	66(1.3)	361(1.0)	1158(1.3)	98(1.6)	451(1.5)	1604(2.2)	85(2.1)	260(2.0)	1300(3.2)	68(2.7)	161(2.5)	1027(4.2)
CHD	31(0.6)	223(0.6)	445(0.5)	91(1.5)	306(1.0)	762(1.1)	117(2.9)	275(2.1)	919(2.3)	97(3.9)	229(3.6)	1004(4.1)
Osteoporosis	65(1.3)	409(1.1)	784(0.9)	80(1.5)	429(1.4)	942(1.3)	98(2.9)	79(3.2)	358(2.7)	107(4.3)	302(4.7)	658 (2.9)
Hypercholesterolaemia	372(7.4)	2619(7.0)	4299(5.0)	464(7.7)	2258(7.4)	4468(6.2)	365(9.0)	1060(8.0)	3025(7.4)	217(8.7)	554(8.6)	1771(7.3)
Body mass index												
Healthy weight/overweight	3714(73.7)	29193(78.4)	63101(72.4)	4420(73.5)	24045(78.4)	51277(70.7)	3045(74.8)	10621(79.9)	28979(71.3)	1926(77.3)	5160(80.0)	17533(71.9)
Obese	1321(26.2)	8026(21.5)	24007(27.5)	1591(26.5)	6609(21.5)	21209(29.3)	1024(25.2)	2665(20.1)	11695(28.7)	565(22.7)	1274(19.8)	6842(28.1)
Smoking status												
Non	2953(58.6)	20360(54.7)	55149(63.3)	3736(62.1)	18185(59.3)	45164(62.3)	2621(64.4)	8121(61.1)	25405(62.5)	1657(66.5)	3986(61.9)	15538(63.7)
Ex	828(16.4)	6179(16.6)	12291(14.1)	1032(17.2)	5682(18.5)	11488(15.8)	788(19.4)	2639(19.8)	6862(16.9)	510(20.5)	1383(21.5)	4507(18.5)
Current	1254(24.9)	10680(28.7)	19668(22.6)	1243(20.7)	6787(22.1)	15834(21.8)	660(16.2)	2526(19.0)	8407(20.7)	324(13.0)	1065(16.5)	4330(17.7)
Deprivation status												
Low	2766(55.0)	20129(54.1)	46550(53.4)	3331(55.4)	16901(55.1)	37981(52.4)	2202(54.1)	7334(55.2)	20809(51.2)	1373(55.1)	3490(54.2)	12275(50.4)
Medium	989(19.6)	7461(20.1)	17679(20.3)	1257(20.9)	6241(20.4)	15055(20.8)	839(20.6)	2717(20.5)	8462(20.8)	506(20.3)	1307(20.3)	5198(21.3)
High	1280(25.4)	9629(25.8)	22879(26.3)	1423(23.7)	7512(24.5)	19450(26.8)	1028(25.3)	3235(24.3)	11403(28.0)	612(24.6)	1637(25.4)	6902(28.3)

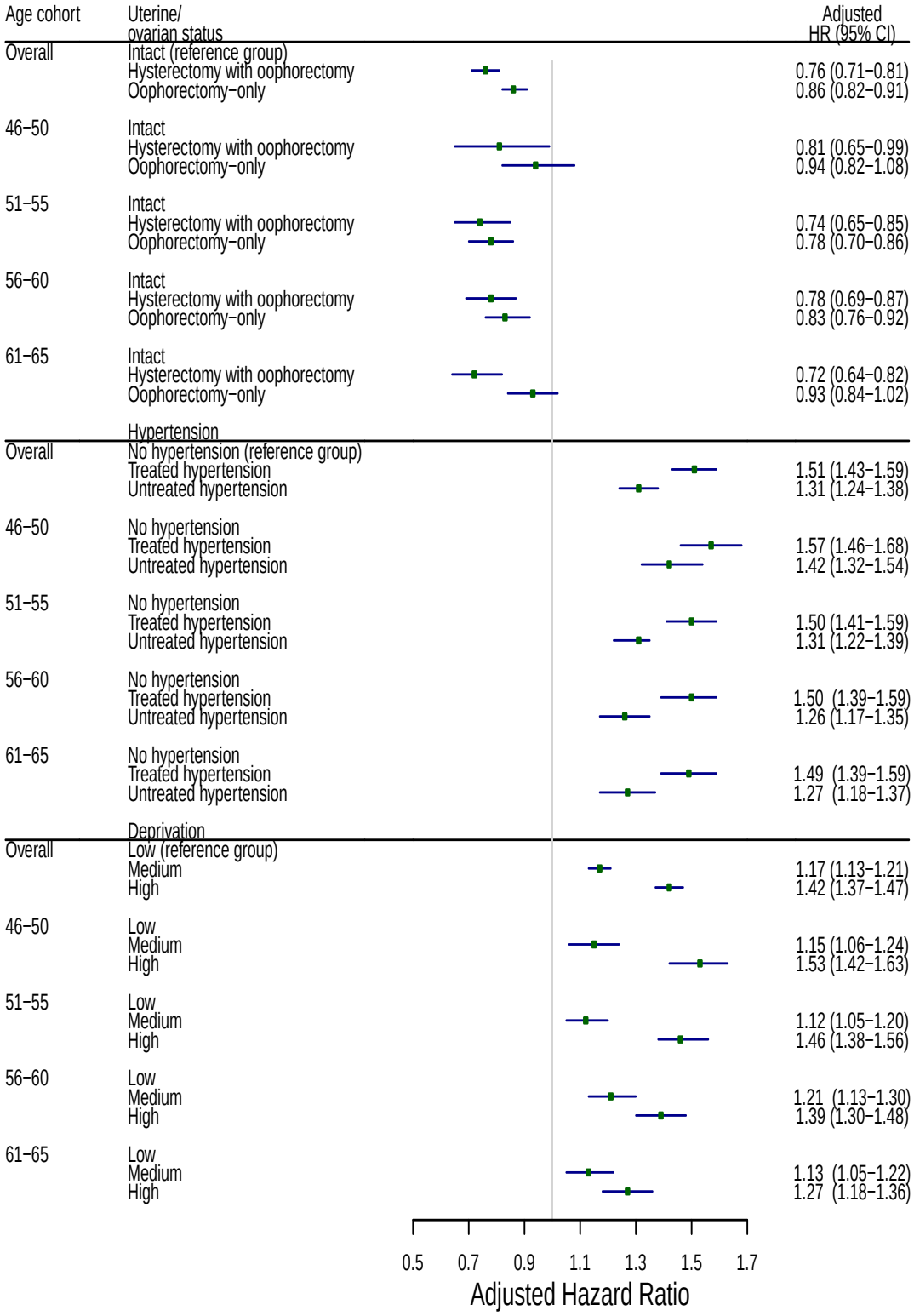

Figure S1: Adjusted effects of hysterectomy/oophorectomy status, hypertension and its treatments, and deprivation status.

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