Relation between hormone replacement therapy and ischaemic heart disease in women: prospective observational study

E Løkkegaard, A T Pedersen, B L Heitmann, Z Jovanovic, N Keiding, Y A Hundrup, E B Obel, B Ottesen

Abstract

Objective To investigate the risk of ischaemic heart disease and myocardial infarction among women using hormone replacement therapy, especially the potential modifying effect of cardiovascular risk factors.
Design Prospective observational study.
Setting Denmark.
Participants 19 898 nurses aged 45 and over completing a questionnaire on lifestyle and use of hormone replacement therapy in 1993.
Main outcome measures All cases of death and incident cases of ischaemic heart disease and myocardial infarction until the end of 1998.
Results Current users of hormone replacement therapy smoked more, consumed more alcohol, had lower self rated health, but were slimmer and had a lower prevalence of diabetes than never users. In current users compared with never users, hormone replacement therapy had no protective effect on ischaemic heart disease (hazard ratio 1.2, 0.9 to 1.7) or myocardial infarction (1.0, 0.6 to 1.7), whereas current users with diabetes had an increased risk of death (3.2, 1.4 to 7.5), ischaemic heart disease (4.2, 1.4 to 12.5), and myocardial infarction (9.2, 2.0 to 41.4) compared with never users with diabetes.
Conclusion Hormone replacement therapy showed no protective effect on ischaemic heart disease, but there was a significantly increased risk of death from all causes and ischaemic heart disease among women with diabetes.

Introduction

The incidence of ischaemic heart disease is declining in the developing world, although it is still the leading cause of death.[1] In women the decline has been attributed to smoking cessation, better diet, and use of hormone replacement therapy, but the decline may be slowed by the increase in sedentary lifestyle, body mass index, and incidence of type 2 diabetes.[2]

Observational studies have shown a protective effect of hormone replacement therapy on cardiovascular disease, although women using hormone replacement therapy tend to have healthier lifestyles than non-users.[3–6] Such a healthy user effect may vary between studies and result in confounding or selection bias.[7] A recent meta-analysis of observational epidemiological studies found no protective effect of hormone replacement therapy on ischaemic heart disease after adjustment for socioeconomic class, income, and education.[7] A randomised controlled trial on the primary preventive effect of hormone replacement therapy found an increased risk of coronary heart disease, especially non-fatal, among women using combined conjugated oestrogen and medroprogesterone acetate.[8] Randomised clinical studies on secondary prevention of ischaemic heart disease among women who had had a myocardial infarction reported an early harmful effect of hormone replacement therapy but an overall neutral effect.[9–11] Questions still remain over the possibility of a risk associated with the European regimens for hormone replacement therapy based on oestradiol-17β in combination with 19-norethisterone derivatives. Few studies have tried to identify subgroups of women who are especially sensitive to hormone replacement therapy.

We examined the association between hormone replacement therapy, based on the Scandinavian regimens, and ischaemic heart disease, myocardial infarction, and total number of deaths among a cohort of Danish nurses. We also determined whether associations between treatment and risk of ischaemic heart disease were modified by risk factors for cardiovascular disease.

Methods

Our study was based on data from a trial on the prevention of osteoporosis and atherosclerosis in Danish nurses.[12] In 1993 all Danish nurses aged 45 years and over who were members of the Danish Nurses' Association (n=23 178) received a comprehensive questionnaire on health, lifestyle, and reproductive conditions, including detailed questions on hormone replacement therapy. Overall, 19 898 (86%) women completed the questionnaire.[12]

Exclusion criteria

Because estimates were stable whatever definition of postmenopausal status was given, we excluded only

Department of Obstetrics and Gynaecology, Hvidovre University Hospital, Kettegård alle 30, DK-2650 Hvidovre, Denmark
E Løkkegaard *research fellow*
A T Pedersen *senior registrar*
Juliane Marie Centre, H:s Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark
B Ottesen *professor*
Department of Biostatistics, Panûm Instituttet, University of Copenhagen
Z Jovanovic *statistician*
N Keiding *professor*
Danish Nurse Study, National Institute of Public Health, DK-2100 Copenhagen, Denmark
Y A Hundrup *master of nursing*
E B Obel *consultant*
Research Unit for Dietary Studies, Institute of Preventive Medicine, Copenhagen University Hospital, DK-1399 Copenhagen, Denmark
B L Heitmann *professor*
Correspondence to:
E Løkkegaard
loekkegaard@dadlnet.dk

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premenopausal women (n=5182). These women were considered premenopausal because they reported monthly bleeding without current use of hormone replacement therapy.

From register based or self reported information we also excluded 336 women with previous ischaemic heart disease, 176 with previous stroke, 1157 with cancer, and 285 with missing information on hormone replacement therapy. Some women had more than one reason for exclusion. We included 13 084 healthy postmenopausal women in the analyses.

Use of hormone replacement therapy and confounders

Information on use of hormone replacement therapy was self reported and classified as current, past, or never use. A further subdivision for current users was based on type of regimen: unopposed oestrogen or combined therapy.

We obtained information on covariates from the questionnaire. Apart from age, which was used continuously, we included other covariates as categorical variables: diabetes (yes or no), other metabolic disease (yes or no), hypertension or hypertension lowering drugs (yes or no), drugs for angina (yes or no), familial predisposition of women to myocardial infarction (yes or no), smoking (never, former, current), alcohol consumption (0.1-14 or >14 units/week), body mass index (<18.5, 18.5-25, 25-30, >30 kg/m^2), leisure time physical activity (heavy >4 hours/week, moderate >4 hours/week, inactive), and self rated health (bad, medium, or good).

End points

We retrieved information on a first episode of ischaemic heart disease from the National Patient Registry of Hospital Discharges, which registers all hospital admissions in Denmark, or from the Cause of Death Register, which registers all causes of death in Denmark. We also linked the data to the Central Person Register, which registers the dates of all deaths. These registers are based on diagnoses from the international classification of diseases system, which changed its coding from the eighth revised version to that of the 10th version in January 1994. Cases of ischaemic heart disease were defined as myocardial infarction, other acute or chronic ischaemic heart disease, angina, or electrocardiographically diagnosed heart disease (ICD codes 410-414 in ICD-8 and codes I20-I25 in ICD-10). For analyses estimating risk of myocardial infarction we used ICD codes 410 and I21-I23. The observation time was until end of 1998.

Statistical methods

We modelled the time to outcomes for ischaemic heart disease by using the Cox proportional hazards model for left truncated and right censored data. We used nurse's age as the underlying time where nurse's age at entry into the study is considered as delayed entry time in the analysis. We used the Cox model to analyse each of the three outcomes of death, ischaemic heart disease, and myocardial infarction, with each of the three variables for use of hormone replacement therapy. For every Cox model we checked the proportional hazard assumption graphically and with Schoenfield residuals. We used univariate analysis to construct a model of the outcome of interest, and we estimated the hazard ratios with 95% confidence intervals for use of hormone replacement therapy, unadjusted for confounders (except age, which is the delayed entry variable). We used multivariate analysis to construct a model of the outcomes, and we estimated the hazards ratios with 95% confidence intervals for use of hormone replacement therapy, adjusted for confounders (familial predisposition, smoking, alcohol consumption, body mass index, physical activity, hypertension, angina, diabetes, thyroid disease, and self rated health). We made a stepwise selection for each outcome to identify the significant confounders where the variable for hormone replacement therapy was kept in the model as the main variable of interest. Thirdly, we analysed the modifying effect of variables by testing the significant covariates in the models for interaction with use of hormone replacement therapy. For significant interactions we present the results stratified on the effect of the variable modifying the effect. We report hazard ratios with 95% confidence intervals for use of hormone replacement therapy at the strata as well as estimates of significant covariates in the model. We chose never users of hormone replacement therapy who had diabetes as the reference to clarify the significance of the modifying effect of diabetes. We excluded missing values from analysis. We performed analyses with SAS version 8.2 and Stata version 7.0.

Results

Of the 13 084 postmenopausal women included in the analyses, 3651 (28%) were current users of hormone replacement therapy at baseline, 1857 (14%) were past users, and 7558 (58%) were never users (table 1). The median duration of use by current users was six years (range 0-43); 1314 women (36%) used unopposed oestrogen and 2154 (59%) used combined therapy mainly based on oestradiol-17β and norethisterone acetate, whereas the remaining 183 (5%) had missing information on their regimen. Only 15 women (0.4%) used conjugated equine estrogens. The median duration of use of hormone replacement therapy for past users was two years (range 0-40). The characteristics of users at baseline differed significantly from non-users as they smoked more, consumed more alcohol, had lower self rated health and lower weight, and had a lower prevalence of diabetes (table 1). Current users had a lower prevalence of hypertension at baseline, and it was more prevalent in past users than never users.

During the observation period there were 971 deaths and 351 cases of ischaemic heart disease (46 fatal and 305 non-fatal). One hundred and eight cases of ischaemic heart disease were myocardial infarctions (32 fatal and 76 non-fatal).

Mortality

In three multivariate analyses, ever use or current use of hormone replacement therapy and current use of combined therapy was not associated with mortality (table 2). Despite this neutral association, diabetes modified the effect of treatment. Current users with diabetes had a significantly increased risk of death (hazard ratio 3.2, 1.4 to 7.5) compared with never users with diabetes (table 3), whereas the risk for ever users

with diabetes was not significantly increased (2.5, 0.7 to 3.4) compared with never users with diabetes. In women without diabetes there was no increased risk of death associated with use of hormone replacement therapy. These increased risks were present even after adjustment for factors associated with an increased risk of death—smoking, hypertension, low body mass index, lower self rated health, angina, no or high alcohol consumption, and low physical activity (table 3).

Table 1 Distribution of covariates at baseline among women using hormone replacement therapy. Values are numbers (percentages)

Covariates	Never user (n=7558)	Past user (n=1857)	Current user (n=3651)
Smoking*:			
Never	2234 (32)	465 (26)	1026 (30)
Former	2117 (30)	582 (33)	1018 (29)
Current	2733 (39)	735 (41)	1421 (41)
Weekly alcohol consumption*:			
None	1699 (24)	345 (19)	543 (16)
1-14 units	4125 (57)	1068 (60)	2105 (60)
>14 units	1398 (19)	379 (21)	861 (24)
Body mass index*:			
<18.5 kg/m^2	255 (4)	64 (4)	96 (3)
18.5-25 kg/m^2	4942 (66)	1180 (63)	2676 (74)
25-30 kg/m^2	1816 (24)	510 (27)	730 (20)
>30 kg/m^2	471 (6)	109 (6)	128 (3)
Weekly physical activity:			
>4 hours hard	1786 (24)	402 (22)	907 (25)
>4 hours moderate	5054 (68)	1293 (70)	2440 (68)
Sedentary	580 (8)	145 (8)	270 (7)
Self rated health*:			
Good	5930 (81)	1310 (73)	2758 (78)
Medium	1201 (17)	421 (23)	666 (19)
Bad	164 (2)	71 (4)	119 (3)
Hypertension*	1320 (18)	366 (20)	551 (15)
Drugs for heart condition	206 (2.9)	52 (2.8)	72 (2.0)
Metabolic disease	498 (6.6)	178 (9.5)	199 (5.5)
Diabetes*	118 (2.5)	28 (1.5)	32 (0.9)
Familial predisposition	397 (5.3)	112 (6.0)	217 (5.9)

*P value <0.05 (χ^2 test).
Missing values not included in percentages.

Ischaemic heart disease

In multivariate analyses, ever users of hormone replacement therapy had a marginally increased risk of ischaemic heart disease compared with never users. The association became insignificant when ever use was subdivided into current use and past use (table 2). The effect of treatment was modified by diabetes, so the overall increased risk of ischaemic heart disease was due to a significantly increased hazard ratio (2.9, 1.1-7.9) among ever users with diabetes at baseline compared with never users with diabetes, whereas there was no increased risk with treatment in women without diabetes (table 3, figure). The hazard ratio was increased further (4.2, 1.4 to 12.5) when current users with diabetes at baseline were compared with never users with diabetes (table 3, figure). These findings were present even after adjustment for smoking, angina or hypertension, low self rated health, and high body mass index—all factors that predicted ischaemic heart disease (table 3). No other significant interactions were found between hormone replacement therapy and the risk factors.

Myocardial infarction

Diabetes also modified the effect of use of hormone replacement therapy in the subset of patients with ischaemic heart disease classified as myocardial infarction (table 3); no overall effect of treatment was found (table 2). Compared with never users with diabetes, there was an increased risk of myocardial infarction among women with diabetes who were current users at baseline (9.2, 2.0 to 41.4; table 3), but for ever users with diabetes the risk was not significantly increased. Otherwise only smoking and hypertension predicted myocardial infarction (table 3).

Discussion

Hormone replacement therapy does not protect women against death, ischaemic heart disease, or myocardial infarction. Rather, the effect of treatment was modified by diabetes, with an increased risk of death from all causes, ischaemic heart disease, and myocardial infarction among women with diabetes using treatment. This effect was not influenced by other risk factors for cardiovascular disease, and we found no other effect modifications.

Harmful effect

Our finding of a harmful effect of hormone replacement therapy among women with diabetes is indicated by another study, where the cardioprotection associated with being female was only seen in women without, not with, diabetes.[1 13] The harmful effect among women with diabetes could be explained by an influence on glycaemic control, although the current literature is inconclusive.[14–18] Although the biological mechanism remains speculative, Koh and coworkers found that oestrogen did not improve the endothelium dependent vasodilation in women with type 2 diabetes despite its favourable influence on lipoprotein concentrations.[19 20] One explanation is that treatment does not benefit the impaired endothelium and that the procoagulative effects of treatment may dominate.

Table 2 Hazard ratios (95% confidence intervals) for risk of death, first ever episode of ischaemic heart disease, and first ever myocardial infarction until end of 1998 according to use of hormone replacement therapy at baseline in 1993. Age is underlying time

	All deaths (n=971)			Ischaemic heart disease (n=351)			Myocardial infarction (n=108)		
Use of treatment	No of women	Age adjusted	Multivariate	No of women	Age adjusted	Multivariate	No of women	Age adjusted	Multivariate
Never:	624	1.00	1.00	198	1.00	1.00	68	1.00	1.00
Ever *v* never	347	1.01 (0.88 to 1.15)	0.95 (0.82 to 1.11)	153	1.25 (1.01 to 1.55)	1.27 (1.00 to 1.60)	40	1.01 (0.68 to 1.50)	0.95 (0.63 to 1.44)
Past *v* never	162	1.04 (0.87 to 1.24)	0.98 (0.81 to 1.19)	72	1.42 (1.09 to 1.87)	1.30 (0.96 to 1.75)	20	1.10 (0.67 to 1.82)	0.93 (0.54 to 1.60)
Current *v* never	185	0.98 (0.82 to 1.16)	0.93 (0.76 to 1.12)	81	1.12 (0.85 to 1.46)	1.24 (0.94 to 1.65)	20	0.93 (0.56 to 1.56)	0.97 (0.57 to 1.65)
Current oestrogen *v* never	101	1.00 (0.81 to 1.25)	0.95 (0.74 to 1.21)	48	1.18 (0.86 to 1.64)	1.33 (0.94 to 1.88)	11	0.97 (0.50 to 1.87)	0.97 (0.49 to 1.93)
Current combined *v* never	69	0.88 (0.68 to 1.13)	0.89 (0.68 to 1.17)	32	1.13 (0.78 to 1.65)	1.25 (0.85 to 1.85)	9	0.99 (0.49 to 2.00)	1.09 (0.54 to 2.21)

Table 3 Hazard ratios (95% confidence intervals) of all deaths, ischaemic heart disease, and myocardial infarction with use of hormone replacement therapy stratified on information about diabetes at baseline

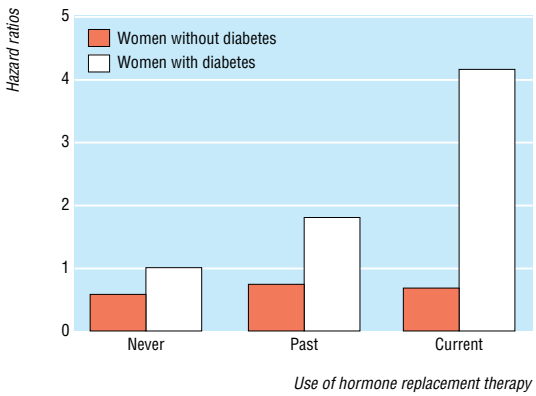
	All deaths (n=971)				Ischaemic heart disease (n=351)				Myocardial infarction (n=108)			
Use of treatment	No of women	Diabetes	No of women	No diabetes	No of women	Diabetes	No of women	No diabetes	No of women	Diabetes	No of women	No diabetes
Never:	23	1.00	593	0.56 (0.35 to 0.91)	8	1.00	187	0.58 (0.27 to 1.26)	3	1.00	65	0.39 (0.12 to 1.26)
Ever *v* never	12	2.54 (0.70 to 3.37)	334	0.53 (0.32 to 0.86)	9	2.90 (1.07 to 7.86)	144	0.70 (0.33 to 1.54)	5	3.87 (0.92 to 16.33)	35	0.32 (0.10 to 1.09)
Previous *v* never	3	0.50 (0.11 to 2.15)	158	0.56 (0.34 to 0.92)	3	1.80 (0.46 to 7.03)	69	0.74 (0.33 to 1.64)	1	1.17 (0.12 to 11.27)	19	0.36 (0.10 to 1.26)
Current *v* never*	9	3.22 (1.38 to 7.46)	176	0.50 (0.30 to 0.82)	6	4.15 (1.38 to 12.45)	75	0.68 (0.30 to 1.49)	4	9.15 (2.02 to 41.44)	16	0.30 (0.09 to 1.08)

Events among missing values on diabetes not included.
*Estimates for significant covariates in multivariate model: death—smoking (never=reference, former 1.20 (0.97 to 1.49), smoker 2.15 (1.76 to 2.62)); hypertension (no=reference, yes 1.32 (1.11 to 1.57)); body mass index (<18.5 kg/m^2=reference, 18.5-25.0 kg/m^2 0.42 (0.32 to 0.53), 25.0-30.0 kg/m^2 0.39 (0.30 to 0.52), >30.0 kg/m^2 0.45 (0.31 to 0.66)); self rated health (good=reference, medium 1.47 (1.24 to 1.74), bad 2.42 (1.80 to 3.26)); angina (no=reference, yes 1.63 (1.23 to 2.15)); weekly alcohol consumption (no=reference, 1-14 units 0.83 (0.70 to 0.99), >14 units 1.10 (0.89 to 1.35)); weekly physical activity (>4 hours hard=reference, >4 hours moderate 1.15 (0.94 to 1.40), sedentary 1.86 (1.43 to 2.41)). Ischaemic heart disease—smoking (never=reference, former 1.08 (0.79 to 1.48), smoker 1.65 (1.23 to 2.21)); hypertension (no=reference, yes 1.61 (1.24 to 2.08)); body mass index (<18.5 kg/m^2=reference, 18.5-25.0 kg/m^2 1.28 (0.62 to 2.61), 25.0-30.0 kg/m^2 1.60 (0.76 to 3.33), >30.0 kg/m^2 2.41 (1.09 to 5.34)); self rated health (good=reference, medium or bad 1.54 (1.20 to 1.97)); angina (no=reference, yes 3.39 (2.35 to 4.89)). Myocardial infarction—smoking (never=reference, former 1.23 (0.65 to 2.30), smoker 3.11 (1.78 to 5.45)); hypertension (no=reference, yes 2.11 (1.38 to 3.23)).

No other observational studies to our knowledge have examined the interaction between hormone replacement therapy and diabetes.[21] Generally, studies have been in healthy postmenopausal women who have had no previous myocardial infarction, diabetes, hypertension, or angina.

To test for a neutral association between hormone replacement therapy and ischaemic heart disease in our sample, we re-examined the data after exclusion of women with diabetes, other metabolic disease, angina, and hypertension. We found no association before and after these exclusions (current users versus never users: 0.82, 0.40 to 1.70 for myocardial infarction and 1.30, 0.92 to 1.85 for ischaemic heart disease).

Our finding of a non-protective effect on ischaemic heart disease agrees with the Women's Health Initiative trial, despite its finding of a significantly increased risk of non-fatal coronary heart disease associated with hormone replacement therapy.[8] The type of treatment used in this trial was, however, different from that used by most of the women in our study. Participants in the Women's Health Initiative trial were randomised to conjugated oestrogens combined with medroxyprogesterone acetate, whereas the Danish nurses mainly used oestradiol-17β combined with norethisterone acetate or levonorgestrel. Twice as many women (4.4%) in the Women's Health Initiative trial were treated for diabetes than in our study. Furthermore, the trial reported no important interaction with background variables, including diabetes, indicating that their study, unlike ours, was unable to show an increased risk associated with hormone replacement therapy among women with diabetes. This may have been due to the sample size.



Hazard ratios for ischaemic heart disease associated with use of hormone replacement therapy stratified on diabetic status

Our finding of a neutral association between hormone replacement therapy and ischaemic heart disease contrasts with most other observational studies, where there was a protective effect of treatment on ischaemic heart disease.[3,4] One explanation is that, unlike other cohorts, the Danish nurses were not healthy users.[4] We previously studied whether nurses in this cohort using hormone replacement therapy differed from non-users and found that current users could not be classed as healthy users as they drank more alcohol at weekends, smoked more, were more sedentary, used the healthcare system more often, and had a lower self rated health than non-users.[22] These findings are similar for Danish women from the general population using hormone replacement therapy. Reasons why Danish women who use hormone replacement therapy cannot be classed as healthy users include free access to medical care and treatment subsidised by the public health system, prompting most menopausal women to seek medical assistance.

Two large Swedish studies found that hormone replacement therapy protected against myocardial infarction; in one, medium dose treatment offered better protection than low dose treatment.[23,24] Both studies were, however, based on prescription registries and were unable to correct for confounders. This prevents a comparison with our results. Also, the Swedish women who used hormone replacement therapy were healthy users.[5]

Study limitations

Our results were based on self reports and may therefore have introduced bias. However, in an earlier study we reported a sensitivity of 78.4% and specificity of 98.4% for use of hormone replacement therapy, showing that never users are correctly classified more often than current users. A non-differential misclassification like this tends to bias the risk estimate towards unity. Therefore we may have overlooked a small protective effect of hormone replacement therapy on ischaemic heart disease. It is unlikely, however, that it would influence the interaction between hormone replacement therapy and diabetes on ischaemic heart disease.

The information on diabetes was also self reported and did not distinguish between type 1 and type 2 diabetes. However, despite the risk that diagnosis may

What is already known on this topic

Observational studies have shown that hormone replacement therapy protects women against ischaemic heart disease

Randomised clinical trials found no such effect

Little attention has focused on identifying subgroups of women who would or would not benefit from treatment

What this study adds

Hormone replacement therapy does not protect against ischaemic heart disease

Women with diabetes who use hormone replacement therapy are at an increased risk of death from all causes and ischaemic heart disease

have been misclassified, we were able to detect a consistent significant interaction between hormone replacement therapy, diabetes, and risk of death from all causes and morbidity from coronary disease. We expect that nurses would give better answers to questions about treatment and illness than women in the general population. Also, the diagnosis is more likely to be correct because nurses have access to methods for measuring glycosuria. We do not believe that Danish doctors considered diabetes an indication for hormone replacement therapy, because the proportion of current users with diabetes at baseline was low.

Contributors: EL carried out the study as part of her PhD project and was responsible for all parts of the research project including writing of the paper. ZJ participated in planning of analyses, conducted statistical analyses, and participated in writing the paper. NK supervised analyses and participated in interpretation and writing the paper. YAH and EBO initiated the Danish nurse cohort and collected data. BLH, BO, and ATP supervised the PhD project and took an active part in all phases of the project, including writing the paper. EL, BLH, ATP, and BO will act as guarantors for the paper.

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Competing interests: BO and ATP have been reimbursed by pharmaceutical companies with an interest in hormone replacement therapy for attending and speaking at several conferences. BO has also received funding for laboratory research. EL received a grant sponsored by Organon.

Ethical approval: The study was approved by the scientific and ethical committees for Copenhagen and Frederiksberg (J.rt (KF) 01-103/93), the Danish Data Protection Agency was notified (1990-1110-270), and the Danish National Board of Health gave permission for access to the National Registry of Hospital Discharges and Death.

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