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

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### 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 decline in incidence of ischaemic heart disease in women in the developing world has been attributed to smoking cessation, better diet, and use of hormone replacement therapy. The decline, however, may be slowed by the increase in sedentary lifestyle, body mass index, and incidence of type 2 diabetes.<sup>1</sup>

Hormone replacement therapy has been shown to have a protective effect on cardiovascular disease, although women using hormone replacement therapy tend to have healthier lifestyles than non-users.<sup>2-4</sup> Other observational studies have found no such

protective effect.<sup>5</sup> A randomised controlled trial on the primary preventive effect of hormone replacement therapy reported an increased risk of coronary heart disease, and randomised clinical studies on secondary prevention of ischaemic heart disease reported an early harmful effect of hormone replacement therapy but an overall neutral effect.<sup>6-9</sup>

We examined the association between hormone replacement therapy 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 an earlier study of Danish nurses.<sup>10</sup> 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.<sup>10</sup>

We excluded 5182 premenopausal women, 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.

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 also obtained information on age, diabetes, other metabolic disease, hypertension or hypertension lowering drugs, drugs for angina, familial predisposition of women to myocardial infarction, smoking, alcohol consumption, body mass index, leisure time physical activity, and self rated health.

We retrieved information on end points from national registries; the National Patient Registry of Hospital Discharges and the Cause of Death Register for a first episode of ischaemic heart disease and the

Central Person Register for dates of death. Cases of ischaemic heart disease were defined as ICD codes 410-414 in ICD-8 and codes I20-I25 in ICD-10 and cases of myocardial infarction were defined as 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. 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 the outcomes of death, ischaemic heart disease, and myocardial infarction with each of the three variables of current, past or never use of hormone replacement therapy. We used univariate analysis unadjusted for confounders and multivariate analysis adjusted for confounders (familial predisposition, smoking, alcohol consumption, body mass index, physical activity, hypertension, angina, diabetes, thyroid disease, and self rated health). We analysed the modifying effect of variables by testing the significant covariates in the models for interaction with use of hormone replacement therapy.

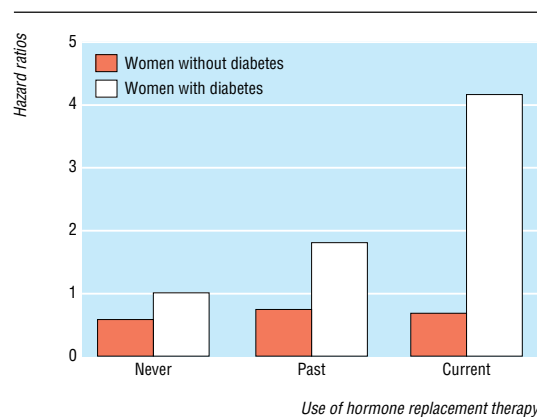
### Results

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. The median duration of use by current users for past users was six years (range 0-43); 1314 women (36%) used unopposed oestrogen and 2154 (59%) used combined therapy mainly based on oestradiol-17 $\beta$  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, and had lower self rated health, weight, and prevalence of diabetes. They also had a lower prevalence of hypertension at baseline—more so 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 of the cases of ischaemic heart disease were myocardial infarctions (32 fatal and 76 non-fatal).

### Mortality

Ever use or current use of hormone replacement therapy and current use of combined therapy was not associated with mortality. However 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. 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



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

rated health, angina, no or high alcohol consumption, and low physical activity.

### Ischaemic heart disease

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. Ever users with diabetes at baseline compared with never users with diabetes, had an overall increased risk of ischaemic heart disease (2.9, 1.1-7.9). In women without diabetes there was no increased risk of ischaemic heart disease associated with hormone replacement therapy (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 (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. 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. 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). For ever users with diabetes the risk was not significantly increased. Otherwise only smoking and hypertension predicted myocardial infarction.

### 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.

The harmful effect of hormone replacement therapy among women with diabetes was indicated in another study,<sup>11</sup> could be explained by an influence on glycaemic control, but the current literature is inconclusive.<sup>12-16</sup> Although the biological mechanism remains speculative, oestrogen seems not to improve endothelium dependent vasodilation in women with type 2 diabetes despite its favourable influence on lipoprotein concentrations.<sup>17 18</sup> One explanation is that treatment does not benefit the impaired endothelium and that the procoagulative effects of treatment may dominate.

The non-protective effect on ischaemic heart disease associated with hormone replacement therapy agrees with the Women's Health Initiative trial.<sup>6</sup> One explanation of our finding, unlike most other observational studies, is that the Danish nurses were not healthy users.<sup>19 20</sup> 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.

### Study limitations

Our results were based on self reports and may have introduced bias. Another study of ours on hormone replacement therapy showed that never users are correctly classified more often than current users. This would tend 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. 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: See bmj.com

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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.r1 (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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## 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

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