

Pre-existing risk factor profiles in users and non-users of hormone replacement therapy: prospective cohort study in Gothenburg, Sweden

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Abstract

Objective To assess whether risk factor profiles for cardiovascular disease differed, before starting treatment, between women who would subsequently use hormone replacement therapy and those who would remain untreated.

Design Prospective population study, initiated in 1968-9, with follow ups in 1974, 1980, and 1992.

Setting Gothenburg, Sweden.

Participants 1201 women born in 1918, 1922, and 1930, representative of women of the same age in the general population.

Main outcome measures Hormone replacement therapy as a function of initial systolic and diastolic blood pressure, waist and hip circumference, waist to hip ratio, body mass index, serum concentrations of cholesterol and triglycerides, smoking status, education, leisure time activity, and socioeconomic group.

Results 179 of the 1202 women (14.9%) used hormone replacement therapy sometime during the 24 year follow up period. Multivariate models indicated that these women had significantly lower blood pressure, had less obesity, and belonged to a higher social group before the start of treatment than women who would remain untreated.

Conclusion Women who would subsequently use hormone replacement therapy were already at lower cardiovascular risk before the start of treatment than women who would remain untreated. Some of the claimed beneficial effects of treatment may thus be explained by women who would use hormone replacement therapy representing a healthier cohort than women who would remain untreated.

Introduction

Oestrogen as hormone replacement during or after the menopause has been widely used since the 1960s, and its use is still increasing.¹ Over the past three decades, many observational studies have reported beneficial effects of postmenopausal hormone replacement therapy on morbidity and mortality from cardiovascular disease. Studies of cardiovascular disease in women showed an almost 50% risk reduction for coronary events in those using hormone replacement

therapy.¹⁻³ Possible biases due to the retrospective design of these studies have, however, been noted, and the need for prospective intervention studies has been emphasised.⁴ Moreover, critics of previous work have suggested that women using hormone replacement therapy represent a special subgroup of the population. One of the previously reported differences between women using and those not using hormone replacement therapy is education, with those receiving treatment representing the more educated group. As higher education is also positively correlated with various indicators of health and wellbeing,⁵ decreased morbidity and mortality among users may be a result of confounding owing to a "healthy user" effect.

Several mechanisms have been proposed for the cardioprotective effects of oestrogen. One is the lipid hypothesis, whereby oestrogen induced increases in high density lipoprotein cholesterol concentration and decreases in low density lipoprotein cholesterol concentration account for the reduction in risk of cardiovascular disease.^{6,7} Other hypotheses concern non-lipid related mechanisms—for example, the effect of oestrogen on platelets and vascular endothelium.⁸

One prospective study recently provided evidence in favour of a healthy user hypothesis.⁹ This study, however, was not sampled on a strict population basis and thus requires confirmation. The heart and estrogen-progestin replacement study, a randomised controlled trial of conjugated oestrogen supplementation in postmenopausal women with established coronary disease, indicates that hormone replacement therapy does not reduce the overall rate of coronary heart disease events.¹⁰ This was a secondary prevention study.

We report from a prospective population based study of women, initiated in 1968-9 in Gothenburg, Sweden, with three additional follow up examinations in 1974-5, 1980-1, and 1992-3.¹¹⁻¹⁴ At each examination women were asked about hormone replacement therapy. Baseline risk factor profile and social status of the women before the introduction of treatment could thus be obtained.

We aimed to assess whether risk factor profiles for cardiovascular disease differed between women who would subsequently use hormone replacement therapy (users) and those who would remain untreated

(non-users). We focused on physical activity, hyperlipidaemia—especially hypertriglyceridaemia—obesity, abdominal obesity, diabetes, hypertension, and smoking¹⁵⁻¹⁷ because these are known risk factors for cardiovascular disease and coronary heart disease in women.

Participants and methods

Study population

In 1968-9, 1462 women in Gothenburg, Sweden, aged 38, 46, 50, 54, and 60, participated in the prospective population study of women in Gothenburg.¹¹ The sampling method was on the basis of date of birth, which with the high participation rate (90.1%) ensured that the participants were a representative cross section of women from the community in the age groups studied.

All women examined in 1968-9 were offered a second examination in 1974-5.¹² Overall, 1302 women attended this examination (89.1% of the women originally examined). In 1980-1 a third examination was conducted¹³ in 1154 participants (78.9% of the women originally examined). Recently a fourth examination was conducted.¹⁴ Of the women originally examined and still alive, 830 (70.1%) participated in this 24 year follow up. Details of the sampling procedure and participation rates at all four examinations are presented elsewhere.¹¹⁻¹⁴ For our study we included the three age groups born in 1918, 1922, and 1930, comprising women who were 50, 46, and 38 years respectively at baseline. These age groups included women who would potentially use hormone replacement therapy during the 24 years of observation.

Information about menstrual status and use of hormone replacement therapy was obtained by means of a standardised interview at all examinations. Women reported if they had ever used single or combined hormone replacement therapy for menopausal symptoms.

Menstrual status was reported at all examinations, and information obtained in 1968-9 was also verified retrospectively in 1974-5. Menopause was defined as more than 12 months without menstruation. To limit our study to a prospective one describing pre-existing characters of women who start hormone replacement therapy, we excluded from the analyses nine women who had already used hormone replacement therapy in 1968-9.

Measured risk factors for cardiovascular disease

Measurements for body weight, body height, body mass index, waist circumference, hip circumference, and systolic and diastolic blood pressure were conducted according to the same protocol at all examinations.¹¹⁻¹⁴ Blood samples were taken after an overnight fast. Serum concentrations of total cholesterol, triglycerides, and glucose were analysed according to standard methods of the laboratory of the Sahlgrenska University Hospital, Gothenburg.

Social and lifestyle related variables

Women were classified according to their smoking habits as: smokers (women who were smoking or had stopped smoking during the previous year); ex-smokers (women who had stopped smoking more than a year before examination); and non-smokers (women who

had never smoked). Participants were classified as being physically active during leisure time if they reported usually spending more than 4 hours a week gardening, running, dancing, playing golf or tennis, or doing similar activities. Women completing 9 years or more of primary or secondary school were classified as having had high education. Finally, women reported their own occupation and, if they were married, their husband's occupation. This information was transformed according to Carlsson's standard occupations grouping system.^{18, 19} For the purposes of our study, we combined group 1 (large scale employers and officials of high or intermediate rank) and groups 2 and 3 (small scale employers, officials of lower rank, and foremen) into a high and medium social group. Groups 4 and 5 (skilled and unskilled workers) were classified as a lower social group. Our study was approved by Gothenburg University's ethics committee.

Statistical methods

For testing the hypothesis of no differences between frequencies (including age) in the analysis, we used the Mantel-Haenszel procedure, an extension of the χ^2 test.²⁰ Multivariate logistic regression was used to simultaneously calculate independent odds ratios for use of hormone replacement therapy as a function of 15 measured risk factors for cardiovascular disease and lifestyle related variables. We tested the significance of nominal categorical variables (smoking) by taking the difference in overall χ^2 model fit of the two models with and without the nominal variable.

Results

Use of hormone replacement therapy

A total of 1192 women born in 1918, 1922, and 1930 were included in our analysis, none of whom at the baseline examination had ever used hormone replacement therapy. Table 1 shows age at first examination in 1968-9 and number and frequency of subsequent use of hormone replacement therapy among the women born in 1918, 1922, and 1930. Around 15% ever used hormone replacement therapy, with a trend to increased usage in younger cohorts.

Measured cardiovascular risk factors

Table 2 shows the mean values of systolic and diastolic blood pressure in the 1968-9 examination. Several of these variables differed significantly between users and non-users, when adjusted for age. Specifically, users had significantly lower systolic and diastolic blood pressure, lower body mass index, and a lower waist circumference before the start of treatment than did non-users. Waist to hip ratio and serum cholesterol and triglyceride concentrations were non-significantly lower in users than in non-users.

Table 1 Details of baseline examination (1968-9) of women who would subsequently use hormone replacement therapy (ever users) and those who would remain untreated (never users) from population study of women in Gothenburg. Values are numbers (percentages) unless stated otherwise

Year of birth	Age (years)	Total No	Ever users	Never users
1918	50	389	25 (8.5)	364 (91.3)
1922	46	431	67 (15.5)	364 (84.5)
1930	38	372	78 (21)	294 (79)

Table 2 Risk factors at baseline (1968-9) in women who would subsequently use hormone replacement therapy (ever users) and those who would remain untreated (never users). Values are mean (SD) unless stated otherwise

Variables	Ever users (n=170)	Never users (n=1022)	P value	
			Age adjusted (n=1192)*	Multivariate (n=1131)†
Systolic blood pressure (mm Hg)	124 (16)	132 (20)	0.0001	0.0001
Diastolic blood pressure (mm Hg)	79 (9)	83 (10)	0.0008	0.05
Waist circumference (cm)	71.1 (7)	73.1 (9)	0.04	0.04
Hip circumference (cm)	98.3 (6)	99.4 (8)	0.17	0.22
Waist to hip ratio (cm/cm)	0.73 (0.05)	0.74 (0.05)	0.06	0.04
Body mass index (kg/m ²)	23.1 (3)	24 (4)	0.04	0.05
Serum concentrations of:				
Cholesterol (mmol/l)	6.63 (1.9)	6.77 (1.1)	0.705	0.46
Triglycerides (mmol/l)	1.15 (0.8)	1.19 (0.5)	0.77	0.93
Glucose (mmol/l)	4.02 (0.6)	4.13 (0.8)	0.21	0.29
Smoking status (%):				
Non-smoker	45	51	0.63	0.65
Current smoker	45	42	0.33	0.41
Ex-smoker	10	7		
Physically active	18	12	0.01	0.28
High and medium socioeconomic status	79	65	0.0002	0.0001
Education >9 years	31	20	0.005	0.07

*Varies from 1192 (maximum) to 1136 (minimum) owing to missing data.

†Number of participants with complete data for all variables.

Social and lifestyle related factors

Table 2 also shows the frequencies of physical activity, education, socioeconomic status, and smoking between the two groups. After adjustment for age there was a statistically significant difference between users and non-users showing that subsequent users were more physically active before starting hormone replacement therapy than were non-users. Users were also more educated and belonged to a higher social group than non-users.

Multivariate analysis

When considering all of the biological and sociobehavioral risk factors simultaneously, the significant predictive value of socioeconomic status and blood pressure was unchanged in the analysis. Physical activity and education, which were previously significant, were not significant in the full model, indicating confounding by socioeconomic status and cardiovascular risk factors. Central obesity (measured as waist to hip ratio and waist circumference) seemed slightly more predictive than body mass index, whereas the reverse had previously been the case in the age adjusted model.

Non-participants

One problem is whether these results are affected by loss to follow up. Despite high initial participation rates (90.1%; 1201 of 1322 women), 254 (21.1%) of these women did not return for any or some of their follow up examinations owing to relocation, refusal, or death. These women were classified as non-users. To determine whether such classification introduced bias to our results, we performed confirmatory analyses on the same three cohorts after removal of those who did not participate after menopause. Multivariate analysis in the participating sample showed that blood pressure and socioeconomic status still differed significantly between users and non-users. Thus, this potential source of error could not explain the healthy user effect.

Discussion

Our study shows that women who would subsequently use hormone replacement therapy (users) already had a better cardiovascular profile before the start of treatment than those women who would remain untreated (non-users). The strongest independent predictors were systolic blood pressure and socioeconomic status. Specifically, a 20 mm Hg increase in systolic blood pressure and a high socioeconomic background each increased the likelihood of hormone replacement therapy use by around 50%.

Several early reports suggesting beneficial effects of hormone replacement therapy during menopause are likely to have reflected confounding by pre-existing differences in the health of users versus non-users. Our findings are consistent with the hypothesis that there has been a self selection of more healthy women for hormone replacement therapy. Women who had lower blood pressure had less obesity and belonged to a higher social class in 1968-9 than other women in the cohort were most likely to become users of hormone replacement therapy. Education and physical activity were also higher among users than non-users but did not retain statistical significance in the multivariate model. Anthropometric variables retained marginal significance in both models.

The healthy user effect shown in our study represents at least two types of selection. Firstly, women from higher social classes and with higher education may select hormone replacement therapy owing to access to more information and better possibilities of obtaining prescriptions. Additionally, prescribers of hormone replacement therapy may have selected their users via prescription practice, and they may have intentionally prescribed to women who were free of cardiovascular disease and known risk factors. Twenty to 30 years ago oestrogen treatment was contraindicated with cardiovascular disease and risk factors because of early studies showing excess myocardial infarction in elderly men taking hormone supplements and thrombosis in women taking oral contraceptives.²¹ Therefore, selection bias probably has been facilitated by both the choice of the women and the prescribers of hormone replacement therapy.

As far as we know this is the first prospective population based study where it has been possible to observe differences in cohorts before starting hormone replacement therapy. The number of users is not high, but the methods of sampling on the basis of date of birth and a high participation rate are strong indicators that the initial participants are representative of all women in Gothenburg of the birth cohorts studied.

Attitudes towards hormone replacement therapy have changed greatly during the past decades among physicians in Western societies. Currently there is a general agreement that climacteric symptoms are oestrogen dependent and effectively alleviated by hormone replacement therapy. Hormone replacement therapy also has an important prophylactic role against osteoporosis.²² It has even been claimed that hormone replacement therapy reduces the risk of coronary heart disease by 50%, and that women with risk factors for cardiovascular disease should also be prescribed hormone replacement therapy

Key messages

- Many retrospective epidemiological studies have shown that hormone replacement therapy reduces the risk of cardiovascular disease
- Results from the prospective population study in Gothenburg show that there were already differences in risk factor profile of women before hormone replacement therapy was considered
- It is too early to recommend hormone replacement therapy for prevention of cardiovascular disease before controlled randomised studies have been performed

prophylactically. On the basis of our study and in the absence of controlled randomised studies showing long term primary preventive effects of hormone replacement therapy, we believe it is too early to establish that kind of recommendation.

Conclusion

We aimed to investigate whether women who would subsequently use hormone replacement therapy had a better cardiovascular risk profile before treatment than did women who would remain untreated. Our results show that users had a lower blood pressure, had less obesity, and belonged to a higher social class before treatment than non-users. This confirms that a large proportion of the "beneficial" effect of hormone replacement therapy may be an artefact of selection.

Contributors: KR, CB, LL, and CB designed and formulated the study hypothesis. CB was the initial coordinator of the population study of women in Gothenburg. CB and LL were coordinators of the follow up examination in 1992-3. KR collected data on hormone replacement therapy. KR, CB, LL, and CB analysed and interpreted the data and contributed to writing the paper. CB will act as guarantor for the paper.

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