Hormone replacement therapy and risk of non-fatal stroke

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Summary

Background The effect of postmenopausal hormone replacement therapy (HRT) on the risk of subtypes of stroke is as yet unclear. To investigate the effect of oestrogen and combined oestrogen-progestagen therapy on the risk of non-fatal haemorrhagic and thromboembolic stroke, we carried out a case-control study.

Methods From the Danish National Patient Register we identified all Danish women aged 45–64 years who had a non-fatal, first-ever cerebrovascular attack during 1990–92. Two age-matched controls were randomly selected for each case from the Danish National Person Register. Important correlates of hormone use and stroke, on which information was obtained from postal questionnaires, were controlled for by multivariate analyses based on log-linear graphical models. The analyses included data on 1422 cases classified in four subtypes of stroke (160 subarachnoid haemorrhage, 95 intracerebral haemorrhage, 846 thromboembolic infarction, 321 transient ischaemic attack) and 3171 controls.

Findings After adjustment for confounding variables and correction for the trend in sales of HRT preparations, no significant associations were detected between current use of unopposed oestrogen replacement therapy and non-fatal subarachnoid haemorrhage (odds ratio 0·52 [95% CI 0·23–1·22]), intracerebral haemorrhage (0·15 [0·02–1·09]), or thromboembolic infarction (1·16 [0·86–1·58]), respectively, compared with never use. Current use of combined oestrogen-progestagen replacement therapy had no significant influence on the risk of subarachnoid haemorrhage (1·22 [0·79–1·89]), intracerebral haemorrhage (1·17 [0·64–2·13]), or thromboembolic infarction (1·17 [0·92–1·47]). A significantly increased incidence of transient ischaemic attacks among former users of HRT and among current users of unopposed oestrogen may to some extent be explained by selection—HRT users being more aware of symptoms than non-users.

Interpretation Unopposed oestrogen and combined oestrogen-progestagen replacement therapy have no influence on the risk of non-fatal thromboembolic or haemorrhagic stroke in women aged 45–64 years.

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Introduction

Stroke is a major contributor to long-term disability and is the third leading cause of death among postmenopausal women in developed countries, after coronary heart disease and cancer. The incidence rate of a first-ever stroke among women aged 45–64 years is 1–2 per 1000 per year.[1] Whereas incidence rates of stroke have changed very little with time, mortality rates have fallen in the past few decades.[2,3] The decline in stroke mortality has been greater for women than for men; this difference between the sexes may be attributable to changing lifestyle patterns and differences in exposure to risk factors for stroke death.

There is convincing evidence of a protective effect of postmenopausal hormone replacement therapy (HRT) against coronary heart disease,[4] but the effect of HRT on the risk of stroke remains controversial. Although a protective effect of oestrogen in physiological doses on stroke is biologically plausible, results from observational studies are conflicting or inconclusive.[5–19] There are few data on the influence of combined HRT regimens and on subtypes of stroke.

The question of whether or not to start HRT is an important concern among perimenopausal and postmenopausal women. Any unclarified effects of the therapy will inevitably influence attitudes and compliance. We therefore undertook a study including a large number of cases, so that there would be sufficient statistical power and valid confounder control, to obtain conclusive evidence about the impact of oestrogen and combined oestrogen-protestagen replacement therapy on haemorrhagic and thromboembolic strokes.

Methods

Denmark has a homogeneous and well-defined population of about five million inhabitants, and there has been limited migration. The Danish Central National Person Register includes all inhabitants. Each individual has a personal registration number and can be followed up from the day of birth throughout life. Linked to this system, there is systematic registration of diseases. The Danish National Patient Register of Hospital Discharges was established in 1976; this is a complete, nationwide register of all hospital discharges in Denmark, including discharge diagnoses according to the WHO International Classification of Diseases (ICD), and patient and hospital unit identification. Access to these national population registers offers exceptional opportunities for epidemiological research on causes of diseases.

Cases

All Danish women aged 45–64 years who survived a cerebrovascular attack during the 3-year period 1990–92 were identified in the Patient Register. Cerebrovascular attacks were defined according to the WHO ICD eighth version as disorders coded by ICD8 430–438. Because first-ever stroke (or transient ischaemic attack) was the object, women registered as having a cerebrovascular disease before the study period were excluded.

The validity of the stroke diagnoses recorded in the Patient Register was investigated in a random sample of 347 case records (15% of the identified cases). Confirmation of the stroke diagnoses was based on evidence of acute onset, specification of localised brain dysfunction, and results of verification procedures such as computed tomography, magnetic resonance imaging, or arteriography. Information was compared with the diagnoses

	1990	1991	1992	1993
Sales in defined daily doses per day				
Systemically administered oestrogens	50 901	53 699	55 560	57 181
Progestagens	21 020	21 351	21 259	20 784
Combined oestrogen-progestagen preparations	57 483	65 279	67 983	75 646
Artificial steroids with combined effect	0	144	2949	4628
Female population aged 45–64 years	573 287	585 202	598 964	612 451

Table 1: **Total sales of HRT preparations in Denmark, 1990–93**

recorded in hospital case records and with the ICD codes transferred to the National Patient Register. Of the stroke diagnoses registered, 4% were tentative diagnoses that were not verified and 2% had been revised subsequently. Misclassifications were caused by ICD coding errors in the hospital case records (5%) and errors arising when ICD codes were transferred to the Patient Register (0·5%).

To obtain permission to contact the stroke patients with a postal questionnaire, we approached the heads of all the 104 hospital departments involved. Lack of permission as well as information on revised or misclassified diagnoses led to exclusions. Departments with fewer than three admissions during the 3-year period were not contacted.

To improve further the validity of the case selection, each case was asked to confirm her diagnosis and the date of discharge according to the information received from the National Patient Register. Furthermore, cases were asked for specific symptoms of the cerebrovascular attack, whether a scan had been done, and whether there had been any previous cerebrovascular events.

Controls

Controls were identified in the Central National Person Register. For each case, two controls were matched by age but were otherwise selected randomly; thus, the current age of a control was within 3 months of that of the matching case at the time of her stroke incident. Women reporting a previous cerebrovascular disease were excluded.

Hormone use and potential confounding factors

Information about HRT was obtained from postal questionnaires which included questions about previous and current hormone use, types of hormones taken (specific names of preparations), regimens, and duration of use. To assist recall, a complete list with photographs of all available products for HRT was included.

HRT was defined as systematically administered hormones for postmenopausal replacement therapy including continuous unopposed oestrogens, sequential/cyclical oestrogen-progestagen regimens, continuous combined oestrogen-progestagen regimens, and artificial steroids with combined oestrogenic, progestagenic, and androgenic effects. Tablets, patches, and preparations for injection were included, but suppositories were excluded because the systemic effects (eg, on the cardiovascular system) were deemed negligible. Regimens of cyclical progestagen only were not included.

Cases were categorised as never-users or former users of HRT, current users of unopposed oestrogen, or current users of combined oestrogen-progestagen therapy. A case was defined as a current user if she was receiving HRT at the time of admission. Use of HRT among women in the control group was that at the time the questionnaires were sent out.

So that the effect of potential confounding cofactors could be analysed, the questionnaires included questions on history of thromboembolic disorders (other than cerebrovascular attacks), treatment of hypertension, heart disease, anticoagulant therapy, diabetes, migraine, former use of oral contraceptives, bodyweight and height, education, marital status, occupational status, smoking habits, physical activity, and other lifestyle characteristics. The questionnaires were sent out in April, 1993.

Non-responders

To assess whether non-responders differed from responders to the questionnaire, we carried out telephone interviews with a randomly selected sample of 100 cases and 100 controls.

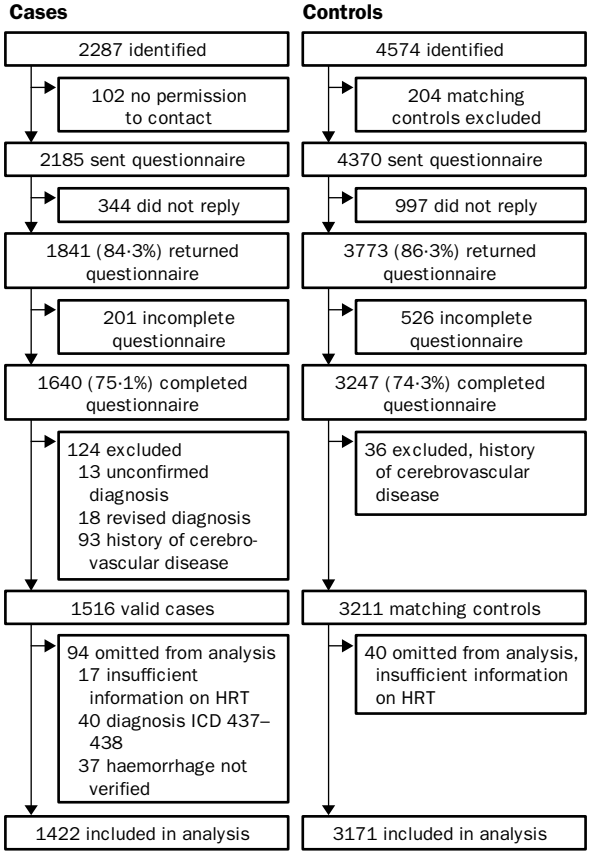

Figure 1: **Flowchart of recruitment and exclusion of cases and controls**

Statistical analyses

The analyses of the case-control data were based on log-linear graphical models by means of the computer program DIGRAM.[20] Graphical models are a subset of the log-linear models for multidimensional contingency tables intended for multivariate statistical analysis of categorical data.[21,22] Graphical models are characterised by conditional independence graphs—a network illustrating statistical associations between the variables included. The independence graph is a visualisation of the statistical model in the same way that path diagrams illustrate causal models. The conditional relations in the graphical model can be assessed by, for example, the χ^2 test or the Goodman-Kruskal γ coefficient.[20] Recursive graphical models include a structure of a linear ordered chain of recursive blocks or levels representing assumptions on a causal or a temporal structure.[23]

The major advantage of graphical modelling over stepwise logistic regression is the information on the collapsibility properties of the model inherent in the graph. Parametric collapsibility is defined by the situation in which certain parameters are the same in the marginal model for a subset of variables as in the joint distribution of the complete set of variables. If a statistical model is collapsible onto the marginal distribution of the exposure-outcome variables, there is no confounding. The structure of the independence graph can be used to distinguish potential confounders and effect modifiers from other variables and mutually. Thus log-linear graphical models provide a useful framework for the initial analysis of data from case-control studies, viewed as a screening procedure to develop information on the qualitative structure of the data set. Graphical modelling is a useful tool to reduce the number of variables and thereby increase the statistical power.

The analyses were carried out in several steps. Initial screening procedures, based on all two-way and three-way interactions, included 21 potential confounding variables to produce a base model for further refinement. After exclusion of variables that did not confound the analyses of HRT and stroke, the initial

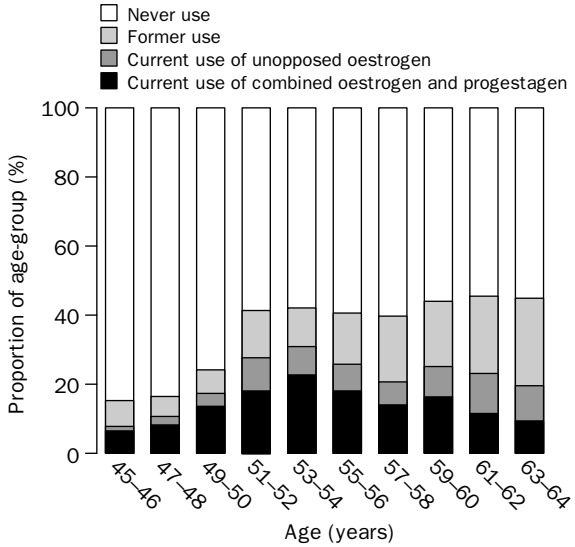

Figure 2: **Use of HRT among study controls by age**

dependence graphs were produced, including important correlates of hormone use and stroke. Tests of significance were done (χ^2 test and for ordinal variables the partial Goodman-Kruskal γ coefficient). The reduced models were reanalysed by log-linear graphical techniques to describe the nature and size of the interaction effects, including identification of effect modifiers represented by higher-order interactions. The risk estimates were calculated as adjusted odds ratios with standard software for analysis of logistic regression models. The reference group chosen was never-users of HRT. To increase statistical power, we included the total number of valid controls in each of the four subanalyses. Since controls were initially matched by age, adjustment for age was indispensable. Age was included in the multivariate model in 5-year age-groups.

Correction for sales trend

Table 1 gives the sale of preparations for HRT in Denmark from 1990 to 1993 estimated in defined daily doses per day, based on figures from Danish Drug Statistics. On the assumption that a third of the progestagens sold are used in a combined regimen with oestrogen, the sale of oestrogens for unopposed use increased by 14·5%, while the sale of oestrogens for combined regimens plus combined oestrogen-progestagen preparations increased by 35·2% from 1990 to 1993. During the same period, the female population aged 45–64 years increased by 6·8%. Cases reported current use of hormones at the time of their stroke event (ie, between 1990 and 1992), whereas controls reported current use at the time they answered the questionnaire in 1993. Calculation of estimates therefore had to account for this bias.

On the assumption that the association between age and distribution of hormone use (never-use, former use, current use of unopposed oestrogens, and current use of combined oestrogen-progestagen therapy) did not change with time, the distribution of unopposed and combined preparations by age-group in 1990, 1991, 1992, and 1993 was estimated by standardisation[22,24] of the observed association between age and hormone use among controls in 1993 to the marginal distributions of age and hormone sales during 1990 to 1993. The standardised estimates were then included in the multivariate regression model, to produce corrected estimates of the adjusted risk estimates.

Variable	Cases	Controls	Odds ratio estimate (95% CI)	
			Adjusted*	Corrected†
HRT				
Never-use	103	1975	1·00	1·00
Former use	21	526	0·78 (0·46–1·30)	0·81 (0·49–1·33)
Current use of unopposed oestrogen	7	235	0·53 (0·23–1·25)	0·52 (0·23–1·22)
Current use of combined regimens	29	435	1·30 (0·84–2·02)	1·22 (0·79–1·89)
Smoking				
Never	30	1101	1·00	..
Former	15	635	1·07 (0·55–2·10)	..
1–10 cigarettes per day	48	629	3·67 (2·20–6·12)	..
11–20 cigarettes per day	63	734	4·37 (2·67–7·14)	..
>20 cigarettes per day	3	49	3·69 (1·06–12·9)	..
Oral-contraceptive use				
Never	78	1580	1·00	..
Former	73	1513	0·84 (0·60–1·20)	..
Hypertension				
None	122	2525	1·00	..
History of hypertension	5	112	1·22 (0·48–3·09)	..
Currently treated hypertension	29	327	2·26 (1·44–3·55)	..
Occupational status				
Employed	102	1593	1·00	..
Housewife	17	432	0·65 (0·37–1·13)	..
Unemployed	10	222	0·60 (0·29–1·22)	..
Retired	29	877	0·42 (0·27–0·67)	..

*Derived from conditional logistic regression taking age, use of HRT, smoking, former use of oral contraceptives, hypertension, and occupation into account.
†Adjusted for confounding factors and corrected for sales trend.

Table 2: **Risk of subarachnoid haemorrhage according to use of HRT and identified risk factors in women aged 45–64 years**

Results

During the period 1990–92, 2584 cases of non-fatal (at discharge), first-ever cerebrovascular attack among women aged 45–64 years were registered in the National Patient Register, which corresponds to an average annual incidence rate of 1·5 per 1000 women aged 45–64. Initially, 270 cases were excluded before case selection was established because they had died (from causes other than stroke) after discharge from hospital. Another 27 cases were excluded because of emigration or missing information on postal address. 4574 controls were matched to the remaining 2287 cases (figure 1).

For further analyses, strokes were classified as intracerebral haemorrhages (ICD 430), subarachnoid haemorrhages (ICD 431), thromboembolic infarctions (ICD 432–434, 436), or transient cerebral ischaemic attacks (ICD 435). The unspecified generalised ischaemic diseases (ICD 437–438) were not included in the final case-control analysis, since other studies of register and case-record data on stroke have reported that these diagnoses are inconsistent, often covering vague or diffuse symptoms such as vertigo, syncope, or dementia.[11]

Among the responding cases, 79% positively stated that a computed tomography or magnetic resonance imaging scan had been done—81% of thromboembolic cases, 87% of haemorrhagic cases, and 65% of cases registered with a transient ischaemic attack. Haemorrhagic cases not positively verified by a scan were excluded.

The final analyses included 160 cases of subarachnoid haemorrhage, 95 cases of intracerebral haemorrhage, 846 cases of thromboembolic infarction, 321 cases of transient ischaemic attack, and 3171 controls.

Figure 2 shows the proportions of control women currently receiving HRT by age-group. At the age of 65, almost 50% of the women were ever-users of HRT.

We found no significant association between HRT and occurrence of subarachnoid haemorrhage (table 2). Confounding factors identified in the log-linear graphical model were smoking habits, former use of oral contraceptives, current treatment of hypertension, and occupational status. A significant dose-response association was found in the risk of subarachnoid haemorrhage according to smoking habits (table 2). Hypertension was significantly associated with subarachnoid haemorrhage and was a substantial confounder in the HRT analysis.

Variable	Cases	Controls	Odds ratio estimate (95% CI)	
			Adjusted*	Corrected†
HRT				
Never-use	64	1975	1·00	1·00
Former use	15	526	1·09 (0·58–2·03)	0·95 (0·51–1·76)
Current use of unopposed oestrogen	1	235	0·18 (0·02–1·27)	0·15 (0·02–1·09)
Current use of combined regimens	15	435	1·22 (0·66–2·23)	1·17 (0·64–2·13)
Oral-contraceptive use				
Never	51	1580	1·00	..
Former	41	1513	0·63 (0·39–1·00)	..
Heart disease				
No	80	2916	1·00	..
Yes	7	91	2·56 (1·00–6·58)	..
Insulin-dependent diabetes				
No	83	2986	1·00	..
Yes	2	28	2·69 (0·62–11·6)	..

*Derived from conditional logistic regression taking age, use of HRT, former use of oral contraceptives, present heart disease, and diabetes into account.
†Adjusted for confounding factors and corrected for sales trend.

Table 3: **Risk of intracerebral haemorrhage according to use of HRT and identified risk factors in women aged 45–64 years**

Women with a job outside the home were at greater risk of subarachnoid haemorrhage than those without employment, housewives, or retired women. The effect of associated social variables, such as years of schooling, education, and type of job, was eliminated when occupational status was included in the model.

Similarly, no significant association was detected between use of HRT and intracerebral haemorrhage (table 3). Confounding factors included former use of oral contraceptives, presence of insulin-dependent diabetes mellitus, and presence of heart disease. Former users of oral contraceptives had a low risk of intracerebral haemorrhage relative to never-users. The presence of heart disease was positively associated with intracerebral haemorrhage (table 3).

Variable	Cases	Controls	Odds ratio estimate (95% CI)	
			Adjusted*	Corrected†
HRT				
Never-use	484	1975	1·00	1·00
Former use	156	526	1·12 (0·88–1·42)	1·08 (0·86–1·35)
Current use of unopposed oestrogen	73	235	1·24 (0·91–1·70)	1·16 (0·86–1·58)
Current use of combined regimens	133	435	1·27 (1·00–1·62)	1·17 (0·92–1·47)
Smoking				
Never	171	1101	1·00	..
Former	84	635	0·76 (0·51–1·12)	..
1–10 cigarettes per day	232	629	2·41 (1·78–3·24)	..
11–20 cigarettes per day	306	734	3·44 (2·61–4·53)	..
>20 cigarettes per day	42	49	6·41 (3·71–11·1)	..
Oral-contraceptive use				
Never	502	1580	1·00	..
Former	318	1513	0·59 (0·49–0·71)	..
Hypertension				
None	502	2525	1·00	..
History of hypertension	69	112	1·71 (0·80–3·67)	..
Currently treated hypertension	198	327	2·59 (1·64–4·07)	..
Heart disease				
No	699	2916	1·00	..
Yes	75	91	2·07 (1·37–3·14)	..
Insulin-dependent diabetes				
No	735	2986	1·00	..
Yes	44	28	5·63 (3·14–10·1)	..
History of thromboembolic attack (non-cerebrovascular)				
No	702	2926	1·00	..
Yes	75	85	2·42 (1·60–3·68)	..

*Derived from conditional logistic regression taking age, use of HRT, smoking, former use of oral contraceptives, hypertension, present heart disease, diabetes, and history of thromboembolic attack into account.
†Adjusted for confounding factors and corrected for sales trend.

Table 4: **Risk of thromboembolic infarction according to use of HRT and identified risk factors in women aged 45–64 years**

For thromboembolic infarction, crude and adjusted odds ratio estimates according to current combined oestrogen-progestagen replacement therapy were slightly raised (table 4), but this association disappeared after correction for the sales trend. No association was found between former use of HRT or current treatment by unopposed oestrogen and thromboembolic infarction. Identified confounding factors including smoking habits, former use of oral contraceptives, treatment of hypertension, presence of heart disease, presence of diabetes, and history of non-cerebrovascular thromboembolic attacks. Smoking was positively associated with cerebrovascular thromboembolic infarction (table 4). Also, a significantly increased risk of thromboembolic infarction was found among women who were being treated for hypertension. However, in women who had never smoked, hypertension did not affect the risk of thromboembolic infarction. History of a non-cerebrovascular thromboembolic event was a strong and significant predictor of cerebrovascular thromboembolic disease and a significant confounder in the HRT analysis. Also presence of heart disease or of insulin-dependent diabetes mellitus was significantly associated with thromboembolic infarction; however, the confounding effect was slight. The risk of thromboembolic infarction was significantly decreased among former users of oral contraceptives.

Variable	Cases	Controls	Odds ratio estimate (95% CI)	
			Adjusted*	Corrected†
HRT				
Never-use	151	1975	1·00	1·00
Former use	85	526	1·83 (1·33–2·51)	1·86 (1·36–2·52)
Current use of unopposed oestrogen	38	235	2·13 (1·41–3·22)	2·11 (1·41–3·17)
Current use of combined regimens	47	435	1·20 (0·81–1·76)	1·25 (0·86–1·82)
Smoking				
Never	64	1101	1·00	..
Former	49	635	1·48 (0·69–2·28)	..
1–10 cigarettes per day	83	629	2·50 (1·70–3·69)	..
11–20 cigarettes per day	108	734	2·82 (1·94–4·10)	..
>20 cigarettes per day	9	49	3·94 (1·73–8·96)	..
Oral-contraceptive use				
Never	178	1580	1·00	..
Former	131	1513	0·77 (0·58–1·01)	..
Hypertension				
None	204	2525	1·00	..
History of hypertension	16	112	1·49 (0·81–2·73)	..
Currently treated hypertension	61	327	2·16 (1·53–3·06)	..
Heart disease				
No	257	2916	1·00	..
Yes	29	91	2·90 (1·74–4·83)	..

*Derived from conditional logistic regression taking age, use of HRT, smoking, former use of oral contraceptives, hypertension, and heart disease, into account.
†Adjusted for confounding factors and corrected for sales trend.

Table 5: **Risk of transient ischaemic attack according to use of HRT and identified risk factors in women aged 45–64 years**

The risk of transient ischaemic attacks was increased among former as well as current users of HRT (table 5). After adjustment for confounding factors and correction for sales trends, the significant associations with former HRT use or current use of unopposed oestrogen persisted. Confounding factors identified included smoking, former use of oral contraceptives, hypertension, and presence of heart disease. A significant trend was found between

smoking and occurrence of transient ischaemic attacks; heavy smokers were at greater risk (table 5). Among women currently being treated for hypertension, there was a significant two-fold increased risk of transient ischaemic attack. Presence of heart disease implied a three-fold increased risk.

Of the 200 non-responders contacted by telephone, 13 cases and 15 controls did not wish to be interviewed. Five cases said they had not had a stroke, and four cases had previously had cerebrovascular disease. Thus, 78 cases and 85 controls were included in the non-responder analysis. No significant differences between responders and non-responders in use of HRT were detected, among cases (χ^2 [3df] 1·5; p=0·694) or controls (χ^2 [3df] 4·3; p=0·234).

Discussion

The population-based design of this study allowed us to estimate the absolute incidence of non-fatal stroke events. No significant effect was found for former use, current use of unopposed oestrogens, or current use of combined regimens on the risk of subarachnoid haemorrhage, intracerebral haemorrhage, or thromboembolic stroke. An approximately two-fold, significantly increased risk of transient ischaemic attack was found among women who had previously used HRT and among current users of unopposed oestrogens. No association between current use of combined hormones and transient ischaemic attack was detected.

The validity of stroke diagnoses in the National Patient Register was confirmed by the systematic review of randomly selected hospital case records. The validity of the stroke diagnoses included in the case-control analysis was improved by exclusion of cases who did not confirm the stroke diagnosis and supported by a high rate of brain imaging scans. If we found out that a stroke diagnosis was revised after the primary hospital admission the case was excluded. These reasons for exclusion accounted for misclassifications found in the systematic review of the hospital case records. The diagnoses of the haemorrhagic and thromboembolic stroke cases included in the analyses were therefore judged to be accurate. However, the diagnosis of transient ischaemic attack is often based on subjective symptoms, which have abated at the time of admission to hospital. The validity of the diagnosis of the cases of transient ischaemic attacks can therefore be questioned.

The validity of self-reported hormone use in a retrospective design depends greatly on accuracy of recall. Recall bias may lead to overestimation or underestimation of the association between exposure and disease, if the cases recall their exposure to a greater or lesser extent than the controls. A woman who experiences a serious incident such as a stroke is likely to reflect on possible causes. Since hormones have previously been suspected of causing thrombosis, many stroke patients will have been asked about intake of hormones, and thus recall may be improved. To assist recall of specific hormone use, a catalogue with photographs of all available preparations of HRT accompanied the questionnaire. Some degree of amnesia often follows a stroke. However, 99% of the responding stroke cases were able to answer the question about whether or not they were using HRT at the time of the event; fewer than 1% chose the questionnaire option "I do not recall". Thus, even though the information from the questionnaires about HRT use could not be independently verified since no uniform external source was available, the self-reports of HRT use seemed to be quite accurate. The women of the control group were asked about hormone use at the time they received the questionnaire; thus recall bias was not relevant.

Since we found no significant difference between responders and non-responders in HRT use, bias due to non-response was apparently negligible.

A prominent concern in assessments of the influence of HRT in observational studies is that hormone users, as a self-selected group, are different from former users as well as from never-users.[25,26] However, in this study, adjustment for the influence of several identified confounding factors did not substantially affect the estimates. Lack of awareness about mechanisms of selection may lead to misinterpretation of the results. However, potential unknown confounders not included in these analyses would have to be very closely associated with the use of HRT and also be strong predictors of stroke to influence the given results. Such an influence cannot be excluded but does not seem likely.

Tables 2–5 give the odds ratio estimates according to each of the identified confounding variables. Alcohol could potentially be a confounder, because a U-shaped association between alcohol intake and incidence of cerebrovascular disease has been demonstrated. However, we found no significant association between alcohol intake and HRT.

These analyses revealed a significantly increased risk of transient ischaemic attack among former users of HRT and current users of unopposed oestrogen compared with never-users. A conceivable explanation of this observation is bias due to differential surveillance. The diagnosis of transient ischaemic attack is based on the history of the attacks and depends on the skill with which the history is taken and interpreted.[27] Symptoms are transient and of varying intensity. Vague symptoms might be neglected by women with less awareness—possibly the same type of women who might tend to ignore a potential need for HRT. If not admitted to hospital, these women would not be available as cases. Greater alertness among hormone users and greater medical attention for women receiving HRT would lead to a higher likelihood of registration of hormone users with presumed transient ischaemic attack. Consequently, the association between this event and HRT would be exaggerated. Cessation of HRT use because of vague neurological symptoms that resulted in transient attack shortly afterwards would increase the association between former hormone use and transient ischaemic attack relative to current use.

Substantial evidence suggests that non-artificial oestrogens in physiological doses have an improving effect on factors that decrease the risk of cardiovascular disease, including stroke; these factors include relaxation of arterial smooth muscle, improvement in cardiac output, and reduction in platelet aggregation, inhibiting the atherosclerotic process.[28] However, oestrogen may have dual and opposite effects on the coagulation system, increasing thrombogenicity.[29] This factor is consistent with the findings of an increased risk of transient ischaemic attack among hormone users.

Several observational studies have investigated the effect of HRT on the risk of stroke (table 6).[5–19] Both increased and decreased risks of stroke in women using oestrogen replacement therapy have been reported. Subtypes of stroke are pathogenetically heterogeneous disorders, as suggested by the different sets of risk factors (tables 2–5).

Reference and year of publication	Design	Definition of exposure*	Definition of outcome†	Cases	Relative risk (95% CI or p)	
					Crude	Adjusted
5 (1978)	Case-control	CEO (ever-use)	Non-embolic infarction	152	· ·	1·13 (0·71–1·77)
			Haemorrhagic stroke	29	· ·	0·86 (0·9–2×10³)
			Embolic infarction	9	· ·	0·49 (0–5·38)
			TIA	16	· ·	2·79 (0·67–11·62)
6 (1979)	Cohort	ORT (current use)	SAH	11	1·6 (0·7–3·8)	· ·
			Other strokes	23	0·9 (0·4–1·8)	· ·
7 (1979)	Cohort	CEO (ever-use)	Stroke syndromes	17	0·2 (p<0·05)	· ·
8 (1980)	Case-control	CEO (current use)	Occlusive stroke	198	1·16 (0·75–1·77)	· ·
9 (1985)	Cohort	CEO (ever-use)	Stroke including TIA	45	· ·	2·27 (p<0·01)
10 (1987)	Cohort	CEO (baseline)	ICD 430–437 (fatal)	8	0·40 (0·01–3·07)	· ·
11 (1988)	Cohort	HRT	ICD 431–434, 436	87	· ·	1·00 (0·5–1·9)
12 (1988)	Cohort	CEO (ever-use)	Stroke (fatal)	63	· ·	0·53 (0·31–0·91)
13 (1989)	Case-control	HRT (ever-use)	Stroke	244	1·20	· ·
14 (1990)	Cohort	HRT	ICD 430–438, 290 (fatal)	23	· ·	0·54 (0·24–0·84)
15 (1991)	Cohort	CEO (current use)	Stroke (all types)	224	0·96 (0·67–1·37)	0·97 (0·65–1·45)
			Ischaemic stroke	113	1·26 (0·78–2·02)	1·46 (0·85–2·51)
			SAH	36	0·80 (0·30–2·10)	0·53 (0·18–1·57)
16 (1993)	Cohort	HRT (ever-use)	ICD 431–434, 436–437			
			Fatal or non-fatal	250	0·68 (0·47–0·98)	0·69 (0·47–1·00)
			Fatal	64	0·41 (0·17–1·03)	0·37 (0·14–0·92)
17 (1993)	Cohort	HRT (baseline)	Acute stroke (ICD 431–436)	256	0·85 (0·75–0·97)	· ·
			SAH	42	1·19 (0·86–1·61)	· ·
			ICH	27	0·68 (0·45–0·99)	· ·
			Thromboembolic stroke (ICD 432–435)	121	0·91 (0·76–1·09)	· ·
18 (1994)	Case-control	HRT (ever-use)	SAH	103	· ·	0·47 (0·26–0·86)
		HRT (current use)		103	· ·	0·38 (0·17–0·84)
19 (1996)	Cohort	HRT (current use)	Stroke (all types)	552	0·93 (0·75–1·16)	1·03 (0·82–1·31)
			Ischaemic stroke	281	1·19 (0·89–1·57)	1·40 (1·02–1·92)
			SAH	144	0·89 (0·59–1·34)	0·90 (0·57–1·41)
This study (1997)	Case-control	ORT	SAH	160	· ·	0·52 (0·23–1·22)
		HRT (combined)	SAH	160	· ·	1·22 (0·79–1·89)
		ORT	ICH	95	· ·	0·15 (0·02–1·09)
		HRT (combined)	ICH	95	· ·	1·17 (0·64–2·13)
		ORT	Thromboembolic stroke	846	· ·	1·16 (0·86–1·58)
		HRT (combined)	Thromboembolic stroke	846	· ·	1·17 (0·92–1·47)

*CEO=conjugated equine oestrogens, ORT=oestrogen replacement therapy. HRT includes combined preparations. †TIA=transient ischaemic attack; SAH=subarachnoid haemorrhage; ICH=intracerebral haemorrhage.

Table 6: **Studies of effect of HRT use on risk of stroke**

However, many of the published observational studies did not discriminate between haemorrhagic or thromboembolic incidents or transient ischaemic attacks. Also, the definition of HRT exposure varied (current use or ever-use). In some studies, hormone use was ascertained at baseline and not updated. A few studies addressed the influence of combined regimens.[13,17,19] This lack of consistency might account for the unclear associations between HRT and risk of strokes (table 6).

Pfeffer and colleagues,[5] in a population-based case-control study, found no influence of oestrogen replacement therapy on the risk of non-embolic infarction, haemorrhagic stroke, embolic infarction, or transient ischaemic attack. However, that study included only 16 cases of transient ischaemic attack. Our finding of no effect of HRT on the risk of subarachnoid haemorrhage is supported by several studies.[6,7,15,19] However, in a population-based case-control study including 103 cases of subarachnoid haemorrhage, Longstreth and colleagues[18] found a reduced risk among postmenopausal women who had ever received HRT compared with never-users.

In a large cohort study in Sweden based on pharmacy records and registers for hospital admissions, a reduced overall risk of stroke among hormone users compared with non-users was found.[17] A significantly reduced risk of intracerebral haemorrhage was detected among all hormone users (odds ratio 0·68 [95% CI 0·45–0·99]), as well as in users of unopposed oestrogens (0·57 [0·30–0·97]). However, no adjustment was made for confounding factors. The risk of thromboembolic stroke was not affected by HRT. No effect of combined regimens was detected on subtypes of stroke, even though the overall risk of stroke was significantly lowered among users of combined oestrogen-progestagen regimens (0·61 [0·40–0·88]).

The latest analysis from the Nurses' Health Study[19] included 552 stroke cases. Neither oestrogen alone nor combined therapy substantially affected the overall risk of stroke in that analysis, although a significantly increased risk of thromboembolic occlusions (not including transient ischaemic attack) was detected among current users of HRT after adjustment for confounding factors (table 6). However, these conclusions were based on observations of a selected population of well-educated women, whereas our findings are based on investigations in a broad population. Most long-term epidemiological data so far, including those from the Nurses' Health Study, have been based on the use of the conjugated equine oestrogens, which are commonly used in the USA. In Europe, including Denmark, human oestradiol is widely used. Hence, our findings, including almost three times as many cases, substantially add to the findings of the Nurses' Health Study.

Lindenstøm and colleagues[30] found a significant

interaction between smoking and HRT as regards the risk of stroke; HRT seems to have a protective effect among smokers only. Analyses by Falkeborn and colleagues[17] showed a significantly lowered risk of stroke with HRT use in women of the youngest age-group compared with women older than 60 years. In our study no higher-order interactions were detected between HRT and smoking or other risk factors as regards the risk of stroke.

The design of our study allowed us to investigate non-fatal stroke events only. All of the cohort studies that assessed the influence of HRT on stroke mortality have shown a protective effect of ever-use of HRT,[10,12,14,16] although not all were statistically significant. This finding could be explained by a reduction in case-fatality due to the influence of HRT. This hypothesis could also to some extent explain our finding of a two-fold increased risk of transient ischaemic attack among HRT users—if users are not protected from cerebrovascular incidents, but do experience milder forms (and are therefore less likely to die from them), one would expect to find an overall unchanged risk of stroke including transient ischaemic attacks, but an altered distribution with fewer fatal stroke events and more cases of transient ischaemic attack among HRT users than among non-users. The results of our study therefore do not exclude a possible protection against fatal stroke events.

Substantial evidence of a protective effect of HRT on coronary heart disease has so far led to the notion of a general beneficial effect of HRT on cardiovascular diseases in postmenopausal women.[4] However, this study confirms that HRT has no effect on the risk of non-fatal haemorrhagic or thromboembolic stroke. Other studies have reported increased risk of venous thromboembolism and pulmonary embolism among current users of HRT.[31–33] A revised and differentiated interpretation of the effects of HRT on the cardiovascular system seems to be inevitable. For this purpose a further integration of epidemiological and biochemical findings with special emphasis on differences in the pathogenesis and the pathophysiology of subtypes of cardiovascular diseases as well as differences in risk profiles is needed.

Contributors

Anette Tønnes Pedersen carried out the study, as part of her PhD project and was responsible for all parts of the research project, including the writing of the paper. Øjvind Lidegaard was responsible for the initial study design and supervised and took active part in all phases of the project, including interpretation and preparation of the paper. Svend Kreiner developed the correction for the sales-trend bias and did the statistical analysis by log-linear graphical models. Bent Ottesen was responsible for overall supervision of the research project, funding, interpretation, and preparation of the paper.

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