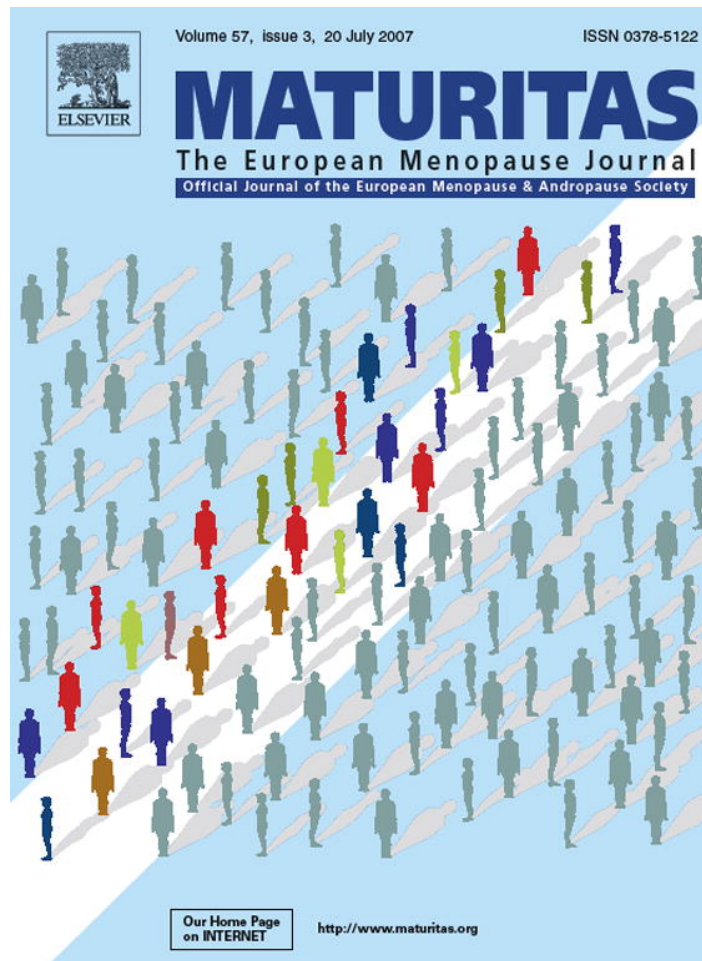


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Hormone replacement therapy and risk for coronary heart disease Data from the CORA-study—A case-control study on women with incident coronary heart disease

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Received 31 July 2006; received in revised form 5 December 2006; accepted 5 January 2007

Abstract

Background: Hormone replacement therapy (HRT) has been suggested to prevent cardiovascular disease, while some intervention studies have shed doubt on this concept. Thus, uncertainty remains whether current HRT use is beneficial as to cardiovascular disease or may even be harmful.

Objectives: This research investigates the association of hormone replacement therapy, risk factors and lifestyle characteristics with the manifestation of coronary heart disease in current HRT users versus never users.

Design: The coronary risk factors for atherosclerosis in women study (CORA-study) provide clinical and biochemical parameters and data on lifestyle in 200 consecutive pre- and postmenopausal women with incident coronary heart disease compared to 255 age-matched population-based controls, of which 87.9% were postmenopausal.

Results: Significantly more controls than cases used currently HRT for a median of 9.5 years (32.9% versus 20.2%), while 50.0% of cases and 42.5% of controls had never used HRT ($p < 0.02$). Compared to women who never used HRT, current users ate less meat and sausage, had a significantly lower BMI and waist-to-hip ratio and a lower prevalence of hypertension, insulin resistance and diabetes. However, current users among cases were often smokers and smoked significantly more cigarettes than never users. In a multivariate analysis the risk of current HRT users for coronary artery disease was 57% lower than the risk of never users (odds ratio 0.428, CI 0.206–0.860, $p < 0.02$). Adjustment for conventional and dietary risk factors revealed neither current HRT use, nor HRT use combined with smoking as independent risk factors.

Conclusions: These data from the CORA-study are not compatible with an adverse impact of hormone replacement therapy on cardiovascular disease, rather support the notion of beneficial effects of HRT on weight, central adiposity, insulin sensitivity and

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blood pressure. Yet, the data do not support the presumption of a general healthy user effect in women on HRT either. Rather, in some women adverse lifestyle habits, especially intense smoking, appear to counteract possible beneficial effects of HRT.
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Keywords: Hormone replacement therapy; Postmenopause; Postmenopausal women; Coronary heart disease; Cardiovascular risk; Risk factors; Cardiovascular protection; Prevention

1. Introduction

Hormone replacement therapy (HRT) has been speculated to postpone cardiovascular disease in postmenopausal women. This is suggested by several long-term observational studies [1–3], but has not yet conclusively been shown by interventional trials, nor has it been excluded though [4,5]. An analysis of data from the Women's Health Initiative on estrogens in postmenopausal women of the relevant age of 50–59 years suggests that cardiovascular events may be reduced by 44% [6]. However, this post hoc subgroup analysis cannot provide proof and is not substantiated by a similar analysis in the arm of the study that combined estrogens with medroxyprogesterone acetate, which, however, may have blunted a beneficial effect of the estrogens [7].

Estrogens exert innumerable effects that may have an impact on the integrity of the vasculature, and estrogen receptors are widely distributed varying in their subspecies among tissues [8]. Also, the effect of estrogens may differ according to age and vascular properties. E.g. in perimenopausal women with intact arteries increased thrombogenesis may not matter and inhibition of cell proliferation may counteract atherogenesis, while in advanced age clotting after plaque rupture may yield severe events and the healing of the ruptured plaque may be disturbed by estrogens. In combined HRT any of the effects may further be modulated by the chosen progestin.

Thus, harm and benefit of HRT are difficult to predict and may vastly differ according to age and health status. This implies that lifestyle and medical care, each may have a great impact on the action of estrogens. Research is complicated since the effects of lifestyle are difficult to quantify and to distinguish from possible effects of estrogens. Even randomized intervention studies may not overcome this problem, since estrogen therapy for climacteric symptoms cannot be blinded versus placebo. Therefore, it appears still appropriate

to investigate further into hormone replacement therapy using information from observational studies with a proper design.

The coronary risk factors for atherosclerosis in women study (CORA-study) provide extensive clinical and biochemical parameters and data on lifestyle in 200 consecutive pre- and postmenopausal women with incident coronary heart disease compared to 255 age-matched population-based controls, most of which were postmenopausal [9]. This research investigates the association of hormone replacement therapy, risk factors and lifestyle characteristics with the manifestation of coronary artery disease in current HRT users versus never and ever users.

2. Methods

2.1. Study design and recruitment procedures

From November 1997 to March 2001 200 consecutive women aged 30–80 years were recruited, who had been admitted with incident CHD to the Department of Internal Medicine. This department serves the catchment area of the University Hospital Hamburg-Eppendorf as primary treatment facility for this disease. The principal inclusion criterion was a first manifestation of CHD (ICD-10 121, 122, 124, 125), i.e. first acute myocardial infarction or first episode of angina or other symptoms suggesting CHD. CHD was verified by angiography. Cases were identified 7 days a week to ensure complete inclusion and to prevent selection bias.

Patients with cancer, severe chronic disease, previous CHD diagnosis or dietary advice regarding CHD were excluded. The participation rate of eligible patients was 100%. For each case two controls were invited through the population registry. If both controls were not eligible because they had deceased, had moved or met the exclusion criteria, another con-

trol was invited. Of 379 eligible controls, 124 (33%) did not participate for various reasons, and 255 (67%) controls were included. To avoid a healthy volunteer effect, visits at home were offered. The study protocol was approved by the Ethical Committee of Hamburg.

2.2. Data collection

All interviews and physical examinations were performed by the same trained investigator. An extensively evaluated, slightly adapted self-administered questionnaire recorded the frequency and portion size of 146 food items eaten during the preceding year [10]. Previous research has shown that the intake of the two food groups fruit and vegetables or meat and sausage reflect dietary habits that affect beneficially or negatively the risk to manifest CHD, respectively [9]. A fasting blood sample was collected from cases and controls, in cases as soon as possible after admission, in women with acute myocardial infarction within at least 24 h, and immediately put on ice. Serum was stored at -80°C . Routine laboratory parameters were determined by standard techniques in the Central Laboratory of the University Hospital. Low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald formula.

Type 2 diabetes mellitus was defined by oral antidiabetic medication or a history of diabetes. Subjects with a homeostasis model assessment (HOMA) insulin resistance score ≥ 3.8 (the lower limit of the upper quartile of a European population) but no history of diabetes were categorised as insulin resistant [11,12]. Hypertension was defined as either taking antihypertensive drugs or having a systolic blood pressure of ≥ 140 mmHg or a diastolic blood pressure of ≥ 90 mmHg [13]. The results of the second and third measurements taken in a sitting position three times after the interviews were averaged [14]. Smokers were defined as current cigarette smokers and former smokers who stopped smoking within the last 2 years, since 63% who reported to have stopped smoking actually had quit less than 1 month ago and much of the coronary risk attributable to smoking disappears gradually within 2 years of quitting [15,16].

Weight was measured in kg to the nearest 0.5 kg. Waist measurement was taken in the middle between the lower rib margin and iliac crest, and the hip circumference was determined over the greater trochanters. Central adiposity was defined by a waist-to-hip ratio

(WHR) ≥ 0.85 [17]. Women were defined as postmenopausal if they had no regular monthly period for more than 1 year or were on hormone replacement therapy. Women were classified as current users of HRT, or as never users, or as ever users if they had used HRT, but not within the last 4 weeks.

2.3. Statistical analysis

The baseline characteristics of the participants were analyzed by univariate chi-square test or Wilcoxon's test, as appropriate. To estimate relative risks, factors statistically significantly different at the 5% level in cases and controls by univariate analyses were entered into logistic regression analysis. Estimates of the relative risks derived from logistic regression were given with 95% confidence intervals. The power was calculated to detect a relative risk of 1.5–1.7 for a marker with a prevalence of 30 or 10%, respectively, in the control group at a power of 80% and a significance of <0.05 , when cases and controls were matched at a ratio of 1:2. All statistical evaluations were performed running the SAS software package, Version 9.1.3.

3. Results

Table 1 shows characteristics of the CHD cases and the control group as to their menopausal status and HRT use. 87.9% of the women had reached postmenopause, 12.2% of whom by ovariectomy. On average the study entry was almost 20 years after menopause. About 50% of cases and controls were ever or current HRT-users with no significant difference in the mode of application. Current users were on HRT for a median of 9.5 years, the majority for at least 3 years, on average cases within 12 years and controls within 14 years. In contrast, among ever users cases and controls used HRT for a median of only 2.5 or 2.0 years since the start of their first HRT, which was on average 21 or 20 years ago, respectively. Current users were about 5 years younger than ever and never users. However, cases and controls differed only in that significantly more controls were current HRT-users. This was also true for the subgroup of ovariectomized women, but the small number did not allow a meaningful statistical analysis.

Table 2 displays anthropometric, clinical and lifestyle factors previously analyzed as to CHD-risk

Table 1
 Characteristics of CHD cases and controls as to menopause and hormone replacement therapy

Parameter	Cases, <i>n</i> = 179	Controls, <i>n</i> = 221	<i>p</i> -Value
Postmenopause (% of total CORA-population)	89.5	86.7	n.s.
Ovarectomy (% postmenopausal women)	13.1	11.4	n.s.
Mean age at menopause (years)	48.5 ± 3.3	48.5 ± 3.2	n.s.
Mean age at study entry (years)	66.2 ± 7.9	67.2 ± 7.7	n.s.
Age <60 years (%)	23.0	19.5	n.s.
Age 60–69 years (%)	38.5	38.0	
Age ≥70 years (%)	38.5	42.5	
Current HRT (%)	20.2	32.9	0.0188
Ever HRT (%)	29.8	24.7	
Never HRT (%)	50.0	42.5	
Current HRT, mean age (years)	61.9 ± 7.3	64.1 ± 7.2	n.s. <0.0001 as to HRT use
Ever HRT, mean age (years)	68.4 ± 7.0	67.9 ± 6.8	
Never HRT, mean age (years)	66.6 ± 8.1	69.1 ± 7.8	
Current HRT, median time of use (years)	9.5 ± 10.5	9.5 ± 9.5	n.s.
Current HRT >3 years (%)	90.0	85.0	n.s.
Median time since starting HRT (years)	12.5 ± 10.0	14.0 ± 10.5	n.s.
Ever HRT, median time of use (years)	2.5 ± 8.3	2.0 ± 5.8	n.s.
Median time since starting HRT (years)	21.0 ± 9.0	20.0 ± 10.0	n.s.
Tablet (%)	61	63	n.s.
Tablet plus other application (%)	19	21	
Patch or injection (%)	20	16	

Values are given as percentage, or mean ± 1 S.D., or median ± the interquartile range (IQR) of the 25th to 75th percentile, respectively.

in the entire CORA-population [9]. Weight, BMI and waist-to-hip ratio were significantly lower in current than in never users. Also, in current users systolic blood pressure was lower and hypertension, insulin resistance and diabetes were less frequent, while the lipid profile was not significantly different. Current users had a lower intake of meat and sausage than never users. When ever and never users combined were compared with current users, the same differences were seen, but the levels of significance were higher (data for ever users not shown).

When cases and controls were separately analyzed as to HRT use, for some differences the significances were lost, supposedly because of smaller numbers. However, among controls current users revealed a significant lower LDL-cholesterol. While in cases, current users smoked significantly more cigarettes. When ever and never users combined were compared to current users, the difference in the rate of smokers became also significant.

Cases and controls differed overall in the same characteristics, whether current or never users were evaluated. This did not materially change, when ever and never users together were compared to current

users. Cases had a higher WHR and lipoprotein(a), a lower HDL-cholesterol and a higher rate of hypertension and insulin resistance. Cases ate more meat and sausage, but only never HRT using cases ate less fruit and vegetables than controls. Cases were more often smokers and smoked significantly more cigarettes.

Multivariate analysis was performed on the subgroup of postmenopausal women employing potential confounders that have previously been identified in univariate analyses [9]. In a conditional logistic regression model, the age-adjusted risk of current HRT users for coronary artery disease was 57% lower as compared to never users (odds ratio 0.428, CI 0.206–0.860, *p* = 0.0196). The risk of ever users was not statistically different from that of never users (odds ratio 1.204, CI 0.657–2.213). Adjustment for the identified conventional and dietary risk factors reduced the odds ratio to 0.70, which, however, was no longer statistically significant (CI 0.37–1.33) (Table 3). Still, there was a trend towards protection, and definitely not towards risk. No case was identified who started HRT within a year before the cardiovascular event. All parameters previously identified to be predictive for CHD remained statistically significant [9]. Also, HRT use combined

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Table 2
Clinical characteristics of cases and controls currently or never on hormone replacement therapy*

Parameter	Current HRT, n = 108	Never HRT, n = 182	p-Value	Cases		p-Value	Controls		p-Value	p-Value, current HRT cases versus controls	p-Value, never HRT cases versus controls
				Current HRT, n = 36	Never HRT, n = 89		Current HRT, n = 72	Never HRT, n = 93			
Anthropometry											
Weight (kg)	67.1 ± 12.6	70.9 ± 13.7	0.03	66.2 ± 12.8	71.0 ± 13.8	n.s.	67.5 ± 12.6	69.2 ± 12.7	n.s.	n.s.	n.s.
BMI (kg/m ²)	24.8 ± 4.2	26.5 ± 4.6	0.0007	24.6 ± 4.4	26.8 ± 4.7	0.02	24.8 ± 4.1	26.3 ± 4.5	0.02	n.s.	n.s.
BMI < 25 kg/m ² (%)	63.9	40.7	0.0004	66.7	39.3	0.02	62.5	41.9	0.02	n.s.	n.s.
WHR	0.84 ± 0.1	0.86 ± 0.09	0.003	0.88 ± 0.1	0.90 ± 0.1	n.s.	0.82 ± 0.07	0.82 ± 0.06	n.s.	0.0005	<0.0001
WHR ≥ 0.85 (%)	34.6	51.9	0.004	62.9	77.3	n.s.	20.8	28.0	n.s.	<0.0001	<0.0001
Lipid profile											
Total cholesterol (mg/dl)	223.7 ± 42.9	230.0 ± 44.4	n.s.	226.3 ± 59.0	225.6 ± 50.9	n.s.	222.4 ± 32.6	234.2 ± 37.0	0.02	n.s.	n.s.
HDL-cholesterol (mg/dl)	60.0 ± 17.4	60.2 ± 19.3	n.s.	49.9 ± 10.6	52.3 ± 17.3	n.s.	65.2 ± 18.0	67.8 ± 18.2	n.s.	<0.0001	<0.0001
HDL-cholesterol < 50 mg/dl (%)	32.1	32.6	n.s.	50.0	51.7	n.s.	22.9	14.3	n.s.	0.0046	<0.0001
LDL-cholesterol (mg/dl)	138.1 ± 40.8	144.7 ± 40.9	n.s.	145.6 ± 54.0	145.2 ± 45.6	n.s.	134.2 ± 31.7	144.3 ± 40.2	0.03	n.s.	n.s.
LDL-cholesterol > 130 mg/dl (%)	52.8	60.7	n.s.	52.8	56.3	n.s.	52.9	64.8	n.s.	n.s.	n.s.
Triglycerides (mg/dl)	125.8 ± 64.6	129.4 ± 72.2	n.s.	148.3 ± 78.0	149.0 ± 84.3	n.s.	114.8 ± 54.4	110.8 ± 84.6	n.s.	0.01	0.0002
Triglycerides > 150 mg/dl (%)	26.0	23.6	n.s.	32.4	31.0	n.s.	22.9	16.5	n.s.	n.s.	0.02
Lipoprotein(a) (mg/dl)	20.8 ± 22.8	26.2 ± 35.2	n.s.	30.5 ± 28.9	33.8 ± 41.1	n.s.	16.1 ± 17.6	18.9 ± 26.6	n.s.	0.03	0.0004
Lp(a) > 25 mg/dl (%)	28.6	32.1	n.s.	43.8	42.7	n.s.	21.2	22.1	n.s.	0.02	0.004
Blood pressure											
Systolic blood pressure (mmHg)	133.2 ± 14.7	139.3 ± 16.2	0.0009	130.7 ± 12.4	136.8 ± 16.1	0.03	134.5 ± 15.7	141.8 ± 15.3	0.003	n.s.	0.02
Diastolic blood pressure (mmHg)	82.6 ± 8.9	84.5 ± 9.1	n.s.	78.9 ± 9.5	81.7 ± 8.2	n.s.	84.5 ± 8.1	87.2 ± 9.2	n.s.	0.004	<0.0001
Hypertension (%)	62.0	78.6	0.008	77.8	89.9	n.s.	54.2	67.7	n.s.	0.02	0.0003
Insulin resistance											
C-peptide	3.1 ± 2.1	4.4 ± 3.7	0.003	4.2 ± 2.9	5.9 ± 4.7	n.s.	2.6 ± 1.2	3.0 ± 1.5	n.s.	0.002	<0.0001
Diabetes/insulin resistance (%)	23.2	40.1	0.003	38.9	56.2	n.s.	15.3	24.7	n.s.	0.0061	<0.0001
Nutrition and smoking											
Fruit/vegetables (g/d)	242.3 ± 115.0	216.9 ± 93.6	n.s.	218.6 ± 99.8	187.0 ± 79.4	n.s.	254.2 ± 120.8	245.6 ± 97.6	n.s.	n.s.	<0.0001
Meat/sausage (g/dl)	76.3 ± 43.3	88.3 ± 42.7	0.01	96.3 ± 42.5	98.5 ± 40.2	n.s.	66.3 ± 40.4	78.6 ± 43.0	n.s.	0.0001	<0.0001
Smoking (%)	34.3	28.6	n.s.	52.8	36.0	n.s.	25.0	21.5	n.s.	0.004	0.03
Cigarettes (per day)	6.4 ± 10.9	4.5 ± 8.4	n.s.	11.8 ± 14.1	6.2 ± 10.0	0.04	3.6 ± 7.6	2.8 ± 6.2	n.s.	0.001	0.017

* Values are given as percentage, or mean ± S.D.

Table 3
Conditional logistic regression analysis on previously established risk factors for CHD and current HRT use

Parameter	<i>p</i> -Value (chi-square)	Odds ratio	95% confidence interval
WHR >0.85	<0.0001	3.17	1.81–5.61
Hypertension	0.002	3.17	1.56–6.72
Diabetes/insulin resistance	0.005	2.36	1.31–4.3
Fruit/vegetables per 100 g	0.007	0.66	0.48–0.88
Lipoprotein(a) >25 mg/dl	0.01	2.08	1.16–3.78
Meat/sausage per 100 g	0.02	2.33	1.14–4.78
HDL-cholesterol >50 mg/dl	0.03	0.49	0.26–0.92
Smoking	0.07	1.76	0.97–3.22
Current HRT	0.28	0.70	0.37–1.33

with smoking, both of which have been suggested to be interacting risk factors, was not an independent predictor of risk.

4. Discussion

The analysis of this case-control study does not support the broadly discussed apprehension of an induction of cardiovascular risk by HRT. If anything, more healthy controls were on HRT, the great majority for many years. The unadjusted odds ratio even points to an appreciable lower risk in women on HRT, which may be due to the HRT per se, to HRT-induced amelioration of risk factors, or concomitant independent beneficial effects. However, as to the latter the results of the CORA-study contradict the common prejudice that HRT is invariably linked to a healthy user effect.

Obviously, the CORA-study is limited by the population size. However, due to the case-control design the power is sufficient to detect differences in most parameters of interest. The absence of an increased risk for CHD in the CORA-study is in accordance with two out of the three large intervention studies or their arms in women of similar age. The notion of cardiovascular risk by HRT is based only on the arm of the WHI, in which estrogens were combined with medroxyprogesterone acetate, while HERS, which used exactly the same combined therapy, even in women at high cardiovascular risk, and the second arm of the WHI that tested estrogen monotherapy showed a neutral outcome as to CHD [4,6,7].

In the CORA-study the lower risk according to the unadjusted odds ratio is in line with a subgroup analysis of the WHI, which at least for an estrogen monother-

apy points to a risk reduction by 44% for women aged 50–59 years at start of the trial [6]. This subgroup indeed is similar to women on HRT in the CORA-study, since women currently on HRT started HRT either during their perimenopause, or shortly thereafter, with a median of 1–2 years after menopause. The early start of HRT appears to be decisive for the cardiovascular benefit, since women starting HRT later in menopause had no or even an adverse effect in the WHI [6,7]. This is substantiated by a recent analysis of the Nurses' Health Study and a meta-analysis of the available randomized trials on HRT, which point to a reduction of cardiovascular disease, when HRT was started before the age of 60 years [18,19].

Women who started HRT later in life had less benefit as to cardiovascular disease and may even face an increased risk in the first year, similar to what has been observed in HERS [4]. In line with the early start of HRT in the CORA-study we were not able to identify a single woman with incident CHD who started HRT in the previous year before the event, but eight such women were among the controls. From the second year on, even women that started HRT late in life have a somewhat decreased cardiovascular risk on HRT according to the meta-analysis. The relative risk reduction apparently decreases with time, however, is still appreciable after more than 10 years of HRT and is associated with reduced mortality after a cardiac event [19,20].

A caveat of the CORA-study certainly is the variety of preparations used for HRT. A detailed analysis according to the drugs used appeared not meaningful, since changes of the medication during previous years were not reliably recalled by the participants and have therefore not been recorded. However, it is rea-

sonable to assume that most women were on combined therapy, which is mandatory for women with intact uterus in Germany since long; thus, only the few hysterectomized women may have been on monotherapy. Because of diverse effects especially of different progestins, but also of estrogens in various applications, the metabolic and clinical consequences may be blurred and are therefore likely to be underestimated. Still, the expected effects of HRT on risk factors are identified in the CORA-study.

A finding of central importance as to cardiovascular risk certainly is the lower waist-to-hip ratio in women on HRT. The impact is clearly reflected by the lower WHR in controls versus cases. Estrogen has been shown to counteract weight gain and particularly central adiposity, also in the large intervention trials, which is supported by the results of the CORA-study [7,21]. One detrimental consequence of central adiposity is insulin resistance, which is counteracted by HRT. The lower rate of insulin resistance in women of HRT in the CORA-study is in line with the large intervention studies, both of which have documented the effectiveness of HRT to prevent diabetes mellitus [21,22].

The CORA-study also documents a positive effect of HRT on blood pressure and the rate of hypertension. The measured blood pressure, however, is confounded by antihypertensives, while the diagnosis of hypertension is not, though. In contrast, the WHI showed an increase in systolic blood pressure, which is explained by the use of medroxyprogesterone acetate [7]. Thus, progestins that convey effective antihypertensive properties may yield an over-average beneficial effect of HRT.

Women on HRT have lower concentrations of cholesterol, LDL-cholesterol and lipoprotein(a), an effect that is weaker with transdermal forms of HRT [23–25]. In the CORA-study statins were used by 64 cases (35.8%) and 23 controls (10.4%). This will mitigate the difference in LDL-cholesterol between current HRT-users and women not using HRT, since more of the latter were cases. Still, in controls the difference of LDL-cholesterol between women on HRT and controls not using HRT reached significance. HDL-cholesterol might have been expected to be higher in women on HRT in agreement with several randomized trials [25]. The reason for a lack of difference may be the high prevalence of smoking in current HRT users, which strongly decreases the HDL-cholesterol.

The data of the CORA-study contradict the commonly held belief that women on HRT follow a healthy lifestyle [26,27]. Controls smoked heavily whether on HRT or not just as cases do, and cases on HRT had even the highest prevalence of smokers and smoked even double as many cigarettes as cases not using HRT. Accordingly, cases using HRT had the lowest HDL-cholesterol and the highest prevalence of low HDL-cholesterol. This prompted us to exclude a detrimental effect on cardiovascular risk by the combination of HRT and smoking using multivariate analysis.

Still, women on HRT tended to be health-conscious in terms of nutrition. In the CORA-study, women on HRT compared with women not using HRT ate more fruit and vegetables and less meat and sausage, a food pattern that has been identified as a strong protective factor in many studies including the CORA-Study [9]. Still, there is a significant difference between cases and controls whether or not using HRT, which is particularly obvious in terms of the intake of meat and sausage, what indicates that many HRT users did not follow an optimal diet.

In conclusion, long-term HRT use is not associated with increased risk for CHD in the CORA-study. This research even supports the notion that HRT can positively affect a number of risk factors like central adiposity, insulin resistance and blood pressure. HRT may even protect from CHD, but adverse lifestyle habits like heavy smoking and a not sufficiently healthy nutrition can offset the beneficial effects of HRT.

Acknowledgements

We are indebted to all participants of the study for their collaboration. We also thank Ms. E. Kohlsdorf and W. Bernigau from the German Institute of Nutrition for their biomathematical assistance. Financial support of the CORA-study was primarily given by the German Stifterverband für die Wissenschaft and to this analysis by Schering Deutschland GmbH.

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