Use of hormone replacement therapy (HRT) among women aged 45–64 years in the German EPIC-cohorts

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1. Background

In the time of transition from pre- to postmenopausal state the ovaries produce lower levels of sex hormones: estrogens, progesterone and testosterone. For

alleviation of climacteric symptoms and prevention of chronic diseases in particular cardio-vascular diseases, hormone replacement therapy (HRT) has been widely recommended. In the 1960s and 1970s, estrogens only preparations were prescribed [1]. Since the end of 1970s a progestin component has been added in order to reduce endometrial hyperplasia and endometrial cancer risk [2].

Before the results of Women's Health Initiative (WHI) were published in 2002, the number of prescriptions increased and the finding regarding adverse outcomes caused debates about the benefits [3]. There is evidence that hormone replacement therapy (HRT) increases breast cancer risk by any year of use [4–6]. The WHI results suggested that estrogen and progestin therapy increases the risk of breast cancer, whereas no increased risk was observed for the use of estrogen alone after an average follow-up time of 5 years [7]. However, the results of observational studies suggest an increase in breast cancer risk also among women with estrogen use alone [8]. Results from the WHI show that compared to the control group, breast cancer cases in the estrogen and progestin group were diagnosed in more advanced stage, indicating that this drug combination stimulates tumour growth or influences breast cancer diagnosis [9]. These findings raised the discussions about the risk and benefits of HRT-use [8], since in the US mainly conjugated equine estrogens (CEE) are prescribed whereas in Germany predominantly non-equine compounds (e.g. 17-β-estradiol) are prescribed. It remains to be discussed how these results from the United States (US) can be transferred to the situation in Germany, because of the differences in the commonly used HRT-regimes. However, also in European study populations long-term HRT-use was associated with increased breast cancer risk [5,10].

In the German MONICA survey, an increase of the HRT-use was observed between 1984 and 1995 [11]. Among Women aged 45–65 years the prevalence increased from 3% in 1984/1985 to 22.6% in 1994/1995. In the latter survey, HRT-use was associated with "healthier" dietary habits, i.e. daily consumption of salad and vegetables, having quit smoking, and regular exercise as well as ever use of oral contraceptives, body mass index (BMI) over 25 kg/m^2 and age. HRT-use was low in alcohol abstainers and persons with low education. However, HRT-users participated more often in cancer screening programs [11].

A similar increase as in the German MONICA survey was observed for the National Health Examination Surveys 1984/1985 and 1998/1999 [12], whereas in a nationwide telephone survey in 2003 the lifetime prevalence of HRT-use was 37.4% in western and 29.2% in eastern Germany [13].

A comparison of HRT-use among women aged 50–59 years participating in the EPIC-study showed that about 45% of women in Heidelberg and in Potsdam were HRT users [14]. Compared to the other EPIC-centers this was the highest prevalence of HRT-use in this age group. Also, among women aged 60 years or older, the prevalence of HRT-use in the German cohorts was about 30% higher than in other centers [14].

The aim of the study was to describe the prevalence and pattern of HRT-use in the German EPIC-cohorts in Heidelberg and Potsdam, and to explore them in relation to other established and potential risk factors for breast cancer and other chronic diseases, such as reproductive history, BMI, alcohol consumption, smoking status, socioeconomic position, and medical conditions such as hysterectomy and oophorectomy.

2. Materials and methods

2.1. Study population

A cross-sectional study was conducted using data of the German EPIC-cohorts in Heidelberg and Potsdam [15]. Both are subcohorts of the European Prospective Investigation into Cancer and Nutrition (EPIC) [16]. In brief, in Heidelberg (western part of Germany) and Potsdam (eastern part of Germany) the recruitment took place between 1994 and 1998 [17]. Subjects were recruited from the general population. Women aged 35–65 years were enrolled. The original cohorts comprised 16,644 women from Potsdam, and 13,613 women from Heidelberg. Women younger than 45 years ($n = 11,483$) and older than 64 years ($n = 1055$) were excluded form this analysis. Women using only topic oestrogen (crème) or Tibolone® were excluded ($n = 15$).

Data were collected by means of a self-administered questionnaire and face-to-face interview. In addition to the assessment of dietary habits, the participants were also asked to provide detailed information about their smoking history, physical activity, subjective

well-being, medical history and use of medications. Anthropometric measures, including weight and height, were taken in standardized manner during the physical examination at the study site.

2.2. Hormone use and other lifestyle characteristics

2.2.1. Lifestyle factors

Education was categorized as low (up to 9 years of schooling without a specific vocational training), middle (10 years of schooling and vocational or technical training) and high (13 years of schooling (grammar school) or a university degree). Smoking status was categorized as never smoker, ex-smoker or current smoker. Body mass index (BMI) was calculated as weight (kg)/height^2 (m) and classified in <25, 25–29.9, and $\geq$30 kg/m^2. Alcohol consumption at recruitment was categorized as abstainer, 1–10 g/day, and >10 g/day.

2.2.2. Reproductive factors

Age at menarche was categorized as <11, 12–14, and $\geq$15 years. Parity was classified as nullipara, 1, 2, 3 and $\geq$4 births at recruitment. Age of 55 years and more was used as proxy for postmenopausal state. The use of oral contraceptives was categorized as ever versus never use. Information on hysterectomy and uni- or bilateral oophorectomy was collected by interview.

Among women aged 45–64 years 2326 (27.8%) women in Heidelberg and 1854 (19.9%) in Potsdam had undergone hysterectomy. Among women with hysterectomy women had also undergone unilateral ($n = 631$) or bilateral ($n = 889$) oophorectomy.

2.2.3. Hormone replacement therapy

Hormone replacement therapy (HRT) was defined as use of hormones for menopausal complaints. The data were collected by means of a standardized questionnaire using the questions: Have you taken hormones for the menopause? If you have taken hormones for the menopause, for how long have you taken it? Current use is defined as use of HRT at baseline examination in 1994–1998.

The reported medications of current use were coded according to the ATC (Anatomic-Therapeutical-Chemical) Code and classified in continuous combined, cyclic combined, estrogen monotherapy, progestin monotherapy, and other monotherapies. Only two women used Tibolone®, a synthetic drug with estrogenic, progestagenic and androgenic properties, and they were excluded from the analysis. For the analyses on HRT-regimes women who applied only topic estrogen ($n = 13$) or did not report on the type of HRT were excluded. Among current HRT-users, for 361 women from Heidelberg and 398 women from Potsdam no information on the type of HRT was available. Among the current users the duration of HRT-use was categorized as $\leq$2, 3–5, and >5 years, and age at the start of HRT was grouped as <44, 45–49, 50–54, and $\geq$55 years.

2.3. Statistical analysis

The associations between the HRT-use and sample characteristics were examined using Mantel–Hansel-test for proportions and Wilcoxon-test for continuous variables. Multivariate logistic regression was used to identify potential indicators of current HRT-use. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated in univariate models and in multivariate models (OR$_{adj.}$) adjusted for potential confounders (age at recruitment, age at menarche, parity, ever-use of oral contraceptives, body mass index (BMI), alcohol consumption, and smoking status) for both centres separately. Since most hysterectomised women use unopposed estrogen, we performed analyses stratified by hysterectomy status. Because the indicators for current and ever HRT-use were comparable, the data for ever HRT-use are not shown.

In order to identify determinants of HRT-use that should be included in multivariate logistic regression analysis, for each centre models with all potential variables, allowing backward selection were conducted. Only variables with p-values <0.10 were included in the final model. Age at menarche was not a significant indicator and was therefore omitted from the final model. All other covariates stated above were retained in the final model.

All statistical tests and corresponding p-values were two-sided, and p-values <0.05 were considered statistically significant. SAS statistical software 9.13 (SAS institute Inc., Cary, NC) was used for all statistical analyses.

Table 1

Baseline characteristics of women aged 45–64 years in the German EPIC-cohorts[a]

Characteristics	Heidelberg (n = 8387)		Potsdam (n = 9317)		p-Value
	n	%	n	%	
Age at recruitment (years)					<0.001
45–49	2201	26.2	2292	24.6	
50–54	2287	22.3	2202	23.6	
55–59	2054	24.5	2819	30.3	
60–64	1845	22.0	2004	21.5	
BMI (kg/m^2)					<0.001
<25	3873	46.2	3896	41.8	
25–30	2964	35.3	3485	37.4	
≥30	1550	18.5	1936	20.8	
Smoking status[b]					<0.001
Never	4509	53.8	6054	65.0	
Ex-smoker	2329	27.8	2007	21.6	
Current smoker	1549	18.4	1251	13.4	
Alcohol consumption (g/day)					<0.001
Abstainer	2264	27.0	1395	15.0	
1–10	3329	39.7	5589	60.0	
>10	2794	33.3	2333	25.0	
Age at menarche (years)[b]					<0.001
≤11	907	10.9	864	9.3	
12–14	5929	71.0	6460	69.4	
≥15	1514	18.1	1981	21.3	
Parity[b]					<0.001
Nullipara	1323	15.8	942	10.1	
1 birth	2083	25.0	2520	27.2	
2 births	3339	40.1	3983	43.0	
3 births	1150	13.8	1352	14.6	
≥4 births	440	5.3	468	5.1	
Ever-use of oral contraceptive[b]					0.007
Yes	6144	73.6	7014	75.4	
No	2204	26.4	2293	24.6	
Hysterectomy[b,c]					<0.001
Yes	2326	27.8	1854	19.9	
No	6056	72.2	7459	80.1	
Oophorectomy[b]					<0.001
Unilateral	507	59.9	610	50.5	
Bilateral	339	40.1	597	49.5	
Current HRT-use[b]					<0.01
Yes	3169	37.9	3330	35.8	
No	5201	62.1	5978	64.2	
Education (years)[b,d]					0.894
Low	3507	41.8	4209	45.2	
Middle	3216	38.4	2924	31.4	
High	1659	19.8	2172	23.3	

[a] Women using only topic oestrogen (crème) or Tibolone were excluded (n = 15).

[b] Numbers in each variable do not add up to total study population in Heidelberg or Potsdam due to missing data.

[c] Includes women with hysterectomy and/or unilateral and bilateral oophorectomy.

[d] Education was categorized as low (up to 9 years of schooling without a specific vocational training), middle (10 years of schooling and vocational or technical training) and high (13 years of schooling (grammar school) or a university degree).

3. Results

Women in Heidelberg were on average slightly younger at enrolment in the study (mean 54.5, S.D. 5.5 years) and gave birth to their first child at older age (mean 24.9, S.D. 4.7 years) than women in Potsdam (mean age at study entry 54.8, S.D. 5.4 and mean age at first birth 23.3, S.D. 3.9 years).

Table 1 shows the baseline characteristic of women aged 45–64 years by centre. In this age group, 37.9% of the women in Heidelberg (HD) and 35.8% of the women in Potsdam (P) reported current use of HRT. Ever-use of HRT was 61.1% and 59.4%, respectively (data not shown). Compared to women from Heidelberg, women from Potsdam were more likely to be overweight (BMI > 25 kg/m^2), never smokers, low alcohol consumers, and were less likely to be nulliparous. Also, women from Potsdam reported an older age at menarche than women from Heidelberg.

Table 2 shows characteristics of current HRT users stratified by type of HRT regimen. For 89% of the Heidelberg-cohort and 88% of the Potsdam-cohort information on the specific HRT preparation was available. Among current users, women were predominantly aged between 50 and 54 years when they started HRT-use (43.1% in HD and 50.5% in P). In Heidelberg, the most often used HRT-medications were estrogen monotherapy (39.3%) and cyclic combined (39.1%) and in Potsdam continuous combined (43.0%) and cyclic combined preparations (29.9%). Regarding duration of HRT-use among current users without bilateral oophorectomy, 40.5% of the women in Heidelberg and 23.7% of the women in Potsdam reported HRT-use longer than 5 years (data not shown). About half of the hysterectomised women used estrogen monotherapy (62.7% in Heidelberg and 44.3% in Potsdam), while among women with intact uterus 26.4% in Heidelberg and 14.5% in Potsdam used estrogen monotherapy.

Tables 3 and 4 present the potential indicators of current HRT-use for women with and without hysterectomy or bilateral oophorectomy. In both centres, current HRT-use increased among hysterectomised women until the age-group of the 55–59 years old (versus 45–49 years OR$_{adj.}$: 3.83, 95% CI: 2.89–5.08 in HD and OR$_{adj.}$: 2.81, 95% CI: 2.11–3.45 in P) and declined thereafter (Table 3). In both cohorts, obesity was a strong inverse indicator for current HRT-use (BMI ≥ 30 versus <25 kg/m^2: OR$_{adj.}$: 0.44, 95% CI: 0.35–0.56 in

HD and OR$_{adj.}$: 0.66, 95% CI: 0.51–0.85 in P). Alcohol consumption was an indicator for current HRT-use in Heidelberg but not in Potsdam. Among women with bilateral oophorectomy older age and obesity were inversely associated with HRT-use in both centers. In Heidelberg, higher alcohol consumption and in Potsdam ever-use of oral contraceptives was associated with higher prevalence of HRT-use, respectively.

Among non-hysterectomised women in Heidelberg (Table 4), women in the age range of 55–59 years were most likely to be current HRT-users (OR$_{adj.}$: 5.71, 95% CI: 4.80–6.80), whereas in Potsdam, women aged 50–54 years were most likely to be current HRT-users (OR$_{adj.}$: 5.06 95% CI: 4.32–5.93). Older age was a stronger indicator for ever HRT-use in women from Potsdam (55–59 years versus 45–49 years OR$_{adj.}$: 4.90, 95% CI: 4.18–5.73) than for women from Heidelberg (OR$_{adj.}$: 1.78, 95% CI: 1.46–2.18) (data not shown). Alcohol consumption (alcohol consumption >10 g/day versus abstainers: OR$_{adj.}$: 1.42, 95% CI: 1.22–1.66 in HD and OR$_{adj.}$: 1.33, 95% CI: 1.11–1.58 in P) was an indicator of current HRT-use in both centres. Also in women without hysterectomy, obese women were less likely to be current HRT-users than women with lower body mass index. In the multivariate models, multiparity was inversely related to current HRT-use in both centres. In Potsdam, highly educated women were more likely to be current HRT-users. No such association was found in Heidelberg.

4. Discussion

Among women aged 45–64 years, approximately 37% were current HRT-users during the time period 1994–1998. Most users were in the age range from 50 to 54 years when they started with the use of HRT. Among ever users, in Heidelberg slightly more women were at ages 45–49 years than in Potsdam (mostly aged 55–59 years). In comparison with other EPIC-centres, the prevalence of HRT in Germany was high [14,18–21]. Compared with data from other international cohorts participating in the WHO-MONICA project with a prevalence range of HRT-use between 0% and 56%, the prevalence in our study population ranges in the upper third [22].

After the publication of the reports from the WHI [3] and Heart and Estrogen/Progestin Replacement

Table 2
Type of hormone regimen among current users of HRT aged 45–64 years ($n = 5740$) in the German EPIC-cohorts[a]

	n	Type of HRT									
		Continuous combined[b]		Cyclic combined		Estrogen mono.		Progestin mono.		Other/unknown/mono other	
		n	%	n	%	n	%	n	%	n	%
Heidelberg											
Women total	2808	500	17.8	1098	39.1	1104	39.3	37	1.3	69	2.5
Women aged ≥55 years	1511	330	21.8	459	30.4	669	44.3	14	0.9	39	2.6
BMI ≥ 30	340	50	14.7	107	31.5	157	46.2	7	2.1	19	5.6
Start HRT aged 45–49 years[c]	957	142	14.8	426	44.5	351	36.7	9	0.9	29	3.0
Start HRT aged 50–54 years[c]	1089	214	19.7	393	36.1	458	42.1	6	0.6	18	1.7
HRT-use >5 years[d]	997	202	20.2	314	31.5	447	44.8	9	0.9	25	2.5
Women without hysterectomy	1806	370	20.5	913	50.6	477	26.4	27	1.5	19	1.1
Women with hysterectomy[e]	1000	129	12.9	184	18.4	627	62.7	10	1.0	50	5.0
Women with bilateral oophoectomy	189	31	16.4	34	18.0	112	59.3	2	1.1	10	5.3
Potsdam											
Women total	2932	1262	43.0	877	29.9	661	22.5	51	1.7	81	2.8
Women aged ≥55 years	1645	752	45.7	397	24.1	436	26.5	17	1.0	43	2.6
BMI ≥ 30	446	192	43.0	133	29.8	104	23.3	9	2.0	8	1.8
Start HRT aged 45–49 years[c]	748	273	36.5	273	36.5	155	20.7	18	2.4	29	3.9
Start HRT aged 50–54 years[c]	1352	599	44.3	411	30.4	289	21.4	20	1.5	33	2.4
HRT-Use >5 years[d]	632	256	40.5	157	24.8	187	29.6	10	1.6	22	3.5
Women without hysterectomy	2138	1047	49.0	684	32.0	309	14.5	48	2.3	50	2.3
Women with hysterectomy[e]	794	215	27.1	193	24.3	352	44.3	3	0.4	31	3.9
Women with bilateral oophoectomy	289	79	27.3	59	20.4	136	47.1	3	1.0	12	4.2

[a] Women without information on type of HRT ($n = 759$) and using only topic oestrogen (crème) or Tibolone were excluded ($n = 15$).
[b] Including free combinations (combining two monotherapies of estrogen and progestins).
[c] Information on age at the start of HRT was available for $n = 2528$ women in Heidelberg and $n = 2670$ women in Potsdam.
[d] Information on the duration of use was available for $n = 2328$ women in Heidelberg and $n = 2401$ women in Potsdam.
[e] Includes women with hysterectomy and/or unilateral and bilateral oophorectomy.

Table 3

Indicators of current hormone use (HRT) among women aged 45–64 years with hysterectomy[a] and bilateral oophorectomy[a] in the German EPIC-cohorts

	Women with hysterectomy[a]								Women with bilateral oophorectomy[b]			
	Univariate analysis				Multivariate analysis[b]				Multivariate analysis[b]			
	Heidelberg (n = 2326)[c]		Potsdam (n = 1854)[c]		Heidelberg (n = 2305)[c]		Potsdam (n = 1842)[c]		Heidelberg (n = 338)[c]		Potsdam (n = 592)[c]	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Age at recruitment (years)												
45–49	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)
50–54	2.54	1.94–3.32	2.08	1.56–2.77	2.88	2.18–3.81	2.18	1.63–2.93	0.81	0.28–2.34	0.77	0.35–1.71
55–59	3.00	2.30–3.90	2.38	1.82–3.12	3.83	2.89–5.08	2.81	2.11–3.45	0.41	0.15–1.13	0.74	0.36–1.51
60–64	1.81	1.39–2.36	1.11	0.84–1.48	2.74	2.04–3.67	1.58	1.16–2.15	0.33	0.12–0.92	0.38	0.18–0.77
BMI (kg/m²)												
<25	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)
25–30	0.80	0.66–0.96	1.02	0.83–1.26	0.81	0.67–0.89	1.02	0.82–1.27	1.14	0.61–2.12	0.69	0.45–1.04
≥30	0.42	0.33–0.52	0.62	0.48–0.79	0.44	0.35–0.56	0.66	0.51–0.85	0.28	0.14–0.53	0.50	0.31–0.79
Parity												
Nullipara	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)
1 birth	0.97	0.72–1.30	0.91	0.66–1.26	0.97	0.71–1.32	0.86	0.60–1.21	0.78	0.36–1.70	0.89	0.51–1.57
2 births	1.21	0.93–1.59	0.97	0.71–1.32	1.14	0.85–1.52	0.86	0.62–1.19	1.05	0.51–2.16	0.80	0.47–1.36
3 births	0.83	0.61–1.14	0.91	0.63–1.32	0.77	0.55–1.08	0.80	0.54–1.17	0.74	0.31–1.79	0.65	0.34–1.25
≥4 births	0.64	0.43–0.97	0.66	0.41–1.07	0.66	0.42–1.02	0.63	0.38–1.05	0.40	0.11–1.37	0.68	0.30–1.52
Ever-use of oral contraceptive												
No	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)
Yes	1.47	1.23–1.75	1.77	1.45–2.16	1.55	1.27–1.88	1.87	1.50–2.33	1.40	0.81–2.39	1.68	1.17–2.43
Smoking status												
Never	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)
Ex-smoker	0.95	0.78–1.15	1.04	0.83–1.30	0.96	0.78–1.18	1.29	0.83–2.02	0.66	0.35–1.26	1.29	0.83–2.03
Current smoker	1.01	0.81–1.27	0.77	0.59–1.01	1.10	0.86–1.40	0.77	0.47–1.27	0.79	0.38–1.65	0.77	0.47–1.27
Alcohol consumption (g/day)												
Abstainer	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)
1–10	1.57	1.29–1.91	1.30	0.98–2.11	1.54	1.25–1.88	1.07	0.84–1.36	3.38	1.81–6.31	1.27	0.79–2.04
>10	1.65	1.33–2.03	1.26	0.94–1.69	1.41	1.13–1.76	0.83	0.62–1.10	2.21	1.16–4.20	0.93	0.53–1.64
Education (years)												
Low	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)
Middle	1.19	1.00–1.42	1.18	0.96–1.46	1.09	0.90–1.31	1.09	0.88–1.36	0.81	0.47–1.42	1.13	0.76–1.70
High	1.32	1.01–1.72	1.22	0.95–1.55	1.07	0.80–1.43	1.14	0.88–1.48	0.51	0.23–1.12	1.59	0.96–2.61

[a] Includes women with hysterectomy and/or unilateral and bilateral oophorectomy.

[b] Adjusted for age at recruitment, education, body mass index, alcohol consumption, smoking status, parity, ever-use of oral contraceptive.

[c] Total numbers differ due to missing data.

Table 4
Indicators of current HRT-use among women aged 45–64 years without hysterectomy in the German EPIC-cohorts

	Univariate analysis				Multivariate analysis[a]			
	Heidelberg (n = 6061)[b]		Potsdam (n = 7463)[b]		Heidelberg (n = 6021)[b]		Potsdam (n = 7420)[b]	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Age at recruitment (years)								
45–49	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)
50–54	3.96	3.38–4.63	4.66	3.99–5.45	4.40	3.74–5.17	5.06	4.32–5.93
55–59	4.30	3.65–5.07	4.02	3.56–4.67	5.71	4.80–6.80	4.89	4.18–5.73
60–64	2.44	2.05–2.90	0.82	1.58–2.22	3.81	3.14–4.61	2.58	2.15–3.09
BMI (kg/m^2)								
<25	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)
25–30	0.88	0.79–0.99	0.79	0.71–0.88	0.81	0.71–0.91	0.79	0.70–0.88
≥30	0.41	0.35–0.49	0.50	0.44–0.58	0.40	0.33–0.48	0.50	0.44–0.59
Parity								
Nullipara	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)
1 birth	1.09	0.93–1.29	1.03	0.86–1.23	1.07	0.90–1.28	0.96	0.79–1.16
2 births	0.98	0.84–1.15	0.94	0.80–1.12	0.86	0.73–1.01	0.89	0.74–1.07
3 births	0.88	0.72–1.08	0.93	0.76–1.13	0.80	0.64–0.99	0.80	0.65–0.99
≥4 births	0.74	0.56–0.99	0.58	0.43–0.77	0.68	0.50–0.92	0.57	0.42–0.77
Ever-use of oral contraceptive								
No	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)
Yes	1.63	1.43–1.86	1.34	1.19–1.51	1.94	1.68–2.25	1.51	1.32–1.73
Alcohol consumption (g/day)								
Abstainer	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)
1–10	1.34	1.16–1.55	1.35	1.17–1.57	1.35	1.16–1.57	1.27	1.08–1.48
>10	1.52	1.32–1.76	1.45	1.23–1.71	1.42	1.22–1.66	1.33	1.11–1.58
Smoking status								
Never	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)
Ex-smoker	1.11	0.98–1.26	0.89	0.79–1.00	1.12	0.97–1.28	0.96	0.84–1.09
Current smoker	1.04	0.90–1.20	0.78	0.67–0.91	1.07	0.91–1.25	0.85	0.72–0.99
Education								
Low	1	(Ref.)	1	(Ref.)	1	(Ref.)	1	(Ref.)
Middle	1.17	1.03–1.32	1.30	1.16–1.46	1.01	0.89–1.16	1.24	1.10–1.40
High	1.02	0.89–1.18	1.21	1.07–1.37	0.90	0.77–1.06	1.20	1.05–1.37

[a] Adjusted for age at recruitment, education, body mass index, alcohol consumption, smoking status, parity, ever-use of oral contraceptive.
[b] Total numbers differ due to missing data.

Study (HERS) II in 2002 [23,24] the prevalence of HRT-use has declined [25,26]. In the WHO-MONICA project, the prevalence of HRT-use in the eastern part of Germany was only 12% in the age group 45–64 years in 1993/1994. The higher prevalence of HRT-use between 1994 and 1998 in EPIC-Potsdam may reflect the increasing numbers until the publication of the WHI results in 2002. In the MONICA-Augsburg study [11] and the KORA-survey [27], both conducted in Augsburg area, western Germany, the prevalence of current HRT-use in 1994/1995 among 45–64-year-old women was lower than in our study cohorts (20% versus 38% and 36%). An analysis of the German National Health Examination Survey of 1998 found a prevalence of 14.5% in the western and 13.1% in the eastern female population aged 45–64 years [12]. In a survey in Pomerania, eastern Germany, the prevalence of ever-use of HRT was lower (28.2%) than in our study [28]. Another representative nationwide survey among women aged 45–60 years revealed the lifetime prevalences of 37.4% in western and 29.2% in eastern Germany [13].

A recent cross-sectional study in Germany reported a prevalence of 35.4% of current HRT-use among postmenopausal women before 2002 [29]. In our study sample, which was not restricted to postmenopausal women only, the prevalence was slightly higher. Older age, i.e. the age between 55 and 59 years was a strong indicator for current and ever HRT-use in both cohorts from Heidelberg and Potsdam. This is in line with the findings of a population-based case-control-study conducted between 2000 and 2002 in Germany, in which the prevalence for ever HRT-use among women 50 years and older was 58% in controls and 61% among cases [29]. Differences in the age groups of women (45–65, ≥40, 31–78, and 45–60 years), the observation period (1993/1993, 1998/1999, 1997–2001 and July 2003) and prevalence period of HRT-use (lifetime, current) may contribute to the variation in prevalence of HRT-use.

In the present study, types of HRT differed by centre. Women in Potsdam were more likely to use continuous combined HRT-preparations. In the EPIC-Heidelberg cohort, 40.5% of women without bilateral oophorectomy used HRT longer than 5 years, while only 27.3% in the EPIC-Potsdam cohort did so. Among ever users aged 45–70 years from the Netherlands 28% long-term users [21] and among German women aged 60–69 years 38.2% were long-term users [28]. The application of oestrogen monotherapy among women with intact uterus was high in both centres (26.4% in HD and 14.5% in P), indicating a long lag-time till recommendations are implemented However, both the duration and the adherence to a specific treatment reflects the interaction between women and physician, which is largely influenced by their personal beliefs and knowledge as well as 'zeitgeist' [1,13,30]. Physicians play an important role in the benefit-risk communication [13,30].

Among non-hysterectomised women, age, alcohol consumption, and former use of oral contraceptives were indicators of current and ever HRT-use in both centres. A higher number of births (3–4 and more births) and higher BMI were associated with less frequent HRT-use. Among hysterectomised women, obesity was also associated with less current HRT-use in both centers. Among hysterectomised women, education as an indicator of socio-economic position was not predictive for current HRT-use and seems to be in line with findings from a cross-sectional study from Denmark, in which no substantial gradient for socioeconomic status in the prevalence of HRT-use was found [31]. In contrast, Mueller et al. observed in the MONICA-cohort in Augsburg that lower educational level was more frequent among non-HRT-users than among HRT-users [11]. Epidemiological studies on HRT-use are influenced by societal factors and the attitudes of physicians, who decide on indication and contraindication [1,13]. Predictors of HRT-use were somewhat similar among hysterectomised and non-hysterectomised women in the present study, whereas different patterns were found for women with bilateral oophorectomy.

Several studies indicated that HRT-use is associated with a healthier lifestyle in general [11,32], however, our observations regarding alcohol consumption and smoking habits do not confirm these findings. In consistency with other reports [11,21,33], higher alcohol consumption (≥10 g/day and even when a cut-off level of ≥30 g/day was used) was an indicator for current and ever HRT-use in non-hysterectomised women in both German EPIC-centres. Alcohol consumption leads to higher plasma estrogen levels [32], which may result in less climacteric complaints and less HRT-use [32]. However, also socio-cultural differences and other medical conditions may influence HRT-use. In our study, current smoking was an indicator for HRT-use only among women from Potsdam without hysterectomy. Smoking has been found to be associated with earlier menopause [34,35] which may be mediated by effects on estrogen production [36]. Also other studies found that current smoking was associated with HRT-use [21,37].

Our observation, that both obesity and a higher number of births are indicators of current and ever HRT-use is in accordance with former reports [11,18,19,21]. Higher levels of circulating estrogens may lead to less climacteric symptoms, and obesity as possible contraindication for HRT-use may have been considered by the prescribing physicians. In line with other studies, use of oral contraceptives in this study was positively associated with HRT-use among women independent of hysterectomy status [11,18,19,38]. The association between oral contraceptive use and HRT-use may reflect the general acceptance of exogenous hormones in a substantial part of the study population.

Some limitations of the present study have to be considered. Since this is a cross-sectional study, due to the

collection of data on potential determinates and HRT-use at the same time, the direction of the associations is uncertain. However, similar indicators were found for current or ever HRT-use, indicating that the association is unlikely to be caused by HRT-use. Women using HRT may differ from non-HRT-users as suggested in several studies [11,18,21,39]. Since these features may also be associated with reduced risk in morbidity and mortality, observational studies on HRT-use and health outcomes such as cardiovascular disease [40] are prone to healthy-user bias [41]. However in our study, no substantial differences regarding a healthier lifestyle of HRT-users were present. Higher alcohol consumption was an indicator for HRT-use in both centres and current smoking was predictive of less current and ever HRT-use in Potsdam. In both study centres, subjects were recruited from the general population, but they may not be representative for Germany in general and therefore caution is needed in generalizing the results [17]. After the publication of adverse effects of HRT, specifically on cardiovascular disease and breast cancer risk in 2002, the prevalence of HRT-use decreased in the US, The Netherlands, and the United Kingdom [25,42,43]. The data for the present study were collected between 1994 and 1998 therefore it is possible that the current patterns of HRT-use may have changed.

In conclusion, compared with other western countries the prevalence of HRT-use among women aged 45–64 years in the German EPIC-cohort was relatively high in the time period 1994–1998. Except for education and smoking status, the indicators for current and ever HRT-use were similar in both cohorts. Regarding the types of HRT-medication differences were found between the two centres. Continuous combined therapies were more frequent in EPIC-Potsdam, whereas continuous combined preparations and estrogens monotherapies were more frequently used in EPIC-Heidelberg. In both study centres, the HRT-use of at least 5 years was high. Future analyses with longer follow-up of the cohorts are needed to explore the effects of different HRT-regimes on the risk of cancer or other chronic conditions.

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