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Marie-Noël Vercambre, Agnès Fournier, Marie-Christine Boutron-Ruault, Françoise Clavel-Chapelon, Virginie Ringa, et al.. Differential dietary nutrient intake according to hormone replacement therapy use: an underestimated confounding factor in epidemiologic studies?. American Journal of Epidemiology, Oxford University Press (OUP), 2007, 166 (12), pp.1451-60. 10.1093/aje/kwm162 . inserm-00170064

HAL Id: inserm-00170064
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Submitted on 13 Aug 2008

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American Journal of Epidemiology 2007;166(12):1451-60

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Differential dietary nutrient intake according to hormone replacement therapy use: an underestimated confounding factor in epidemiological studies?

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Abstract

Observational studies and randomized controlled trials have produced divergent results concerning the effect of hormone replacement therapy (HRT) on cardiovascular disease and, to a lesser extent, dementia. Residual confounding (confounding that remains even after adjustment for various socioeconomic and lifestyle factors) is one explanation that has been offered for these divergent results. The authors used data collected between 1990 and 1995 from 6,697 French women ages 61-72 participating in a prospective cohort study to explore the hypothesis that nutritional intake varies according to HRT use, and thus may be a source of residual confounding. After the authors adjusted for health and lifestyle factors, HRT users, compared with never users, had significantly higher intakes of alcohol, ω3 fatty acids, vitamins B6, B12, and D, and phosphorus, and a lower intake of starch. These differential nutrient intakes were related to differences in eating habits. In particular, HRT users in the studied sample, compared with non-users, ate significantly more fish. Most of the dietary differences were seen in both early-users and delayers of HRT. To limit residual confounding in observational studies, dietary factors may be important parameters to be taken into account in analyses of HRT use and health outcomes.

bias (epidemiology); cohort studies; confounding factors (epidemiology); diet; hormone replacement therapy; nutritional status; observation studies; randomized controlled trials

Abbreviations: HRT, hormone replacement therapy

Until recently, hormone replacement therapy (HRT) was promoted and prescribed widely. This position of the medical community rested not only on the efficacy of HRT in reducing vasomotor symptoms (1) and improving bone density (2) but also on some evidence (mainly based on observational studies) for cardioprotection (3-6) and, to a lesser extent, cognitive protection (7-9). However, results of both epidemiological and clinical studies in the past decade have challenged the concept that HRT has an overall beneficial effect (10-12). In particular, randomized controlled trials on HRT have pointed out neutral or increased risks for cardiovascular disease (12,13) and dementia (14,15), findings strongly divergent from the results of earlier observational studies.

From an epidemiological viewpoint, this striking discrepancy raises interesting questions, which have been extensively discussed in the literature (16-21). In particular, the healthy HRT user bias was put forward by some authors to partly explain the divergent findings with respect to cardiovascular disease and HRT. Posthuma et al (22) concluded in 1994 that unintended selection of relatively healthy women for estrogen therapy may have influenced the reported beneficial effect of HRT on cardiovascular disease. Mattews et al (23) showed in 1996 that women who elect to use HRT have a better cardiovascular risk factor profile prior to HRT use than women who subsequently do not use this treatment during menopause. Persson et al (24)

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This is a pre-copy-editing, author-produced PDF of an article accepted for publication in* American Journal of Epidemiology *following peer review. The definitive publisher-authenticated version* Vercambre et al. *Am. J. Epidemiol.*.2007; 166: 1451-1460 *is available online at: http://aje.oxfordjournals.org/cgi/content/full/166/12/1451

also called attention to the important and complex risk of selection biases in studies of HRT effects. Finally, Grodstein (16) includes the healthy user bias in a detailed list of potential explanations for the discrepancy between randomized controlled trials and observational studies regarding HRT and coronary heart disease. Differences in population, in treatment patterns and in study designs were also highlighted. More recently, Prentice (20) and others (25,26) suggest that the apparent discrepancy may be substantially explained by confounding.

In this context, to adjust adequately in the analyses, identifying factors related to both health outcomes and HRT use is helpful before conducting epidemiologic studies. Most studies of user characteristics have focused on medical history and socioeconomic factors, although eating habits and consequently nutrient intakes may also play a role. Indeed, women with particular food patterns, such as those who follow a low-fat diet or a Mediterranean diet, may selectively use postmenopausal hormones. These differences in eating habits, if present, may result in differential nutrient intakes. If this heterogeneity is ignored in the analysis of HRT effect, the estimate of the relative risk of a disease for which nutrition (but not necessarily HRT) plays a role could then be biased.

We hypothesized that HRT users compared with never-users tended to have different nutrient intakes with profiles in accordance with those described as protective for cardiovascular disease and dementia. For instance, it has been suggested that increased intake of various vitamins or minerals could reduce the incidence rate of vascular disease (27-32) and of cognitive decline or dementia (33). To illustrate the relevance of such hypothesis, we examined the association between HRT use and nutrition in the elderly subpopulation of a cohort of French women of the National Education System

MATERIALS AND METHODS

Population

The Etude Epidémiologique de Femmes de la Mutuelle Générale de l'Education Nationale (E3N) Study is a prospective cohort study primarily investigating cancer risk factors (34,35) among women covered by the national teachers' health insurance plan in France. The study was approved by the Bicêtre Hospital Review Board and the French National Commission for Data Protection and Privacy. Since June 1990, after having given informed consent, study participants have been asked at approximately 24-month intervals to complete self-administered questionnaires including a variety of lifestyle characteristics. We limited our study to the oldest stratum of the study cohort (10,040 women born in 1925-1930) for whom a specific aging questionnaire is being developed. These women were 61-72 years when providing dietary data and 90.7 percent of them were at least 10 years' postmenopause. The passing of time reduces the risk of false classification of a HRT-delayer among never-users and allows a better identification of different use patterns.

Data Collection

Data analyzed here come from the three first questionnaires. Information on lifetime use of hormonal treatments was first recorded in January 1992 (second questionnaire). To facilitate accurate recall, a booklet presenting an extensive list and color photographs of the hormonal treatments marketed in France was mailed to all study participants. Information was updated in each subsequent questionnaire.

The dietary questionnaire analyzed in the present study was sent, along with the third questionnaire, to study cohort participants between June 1993 and July 1995. The dietary questionnaire was sent to the 9,459 women born in 1925-1930 (94.2 percent of the 10,040 women in this age group) who were still included in the study, with two reminders to nonresponders. A total of 7,487 completed questionnaires (79.2 percent) were returned.

The dietary questionnaire was sent with a booklet of photographs to facilitate the estimation of portion sizes. The questionnaire covered daily consumption of 238 food items. Both the questionnaire and the illustrated booklet were validated previously (36, 37) on a sample of 115 women (aged 36-65 years), taking as reference the average of twelve 24-hour dietary recalls obtained at monthly intervals over a 1-year period. A high proportion of subjects (76 percent for foods and 72 percent for nutrients on average) were classified in the same or adjacent quintile for the dietary questionnaire and the 24-hour recalls.

Average daily dietary intakes of macro- and micronutrients were estimated based on the dietary questionnaire by using a food composition table derived from the French national database (38). Women for whom values for the energy intake/energy requirement ratio (calculated taking age, weight and height into account) were extreme (in the top or bottom of the entire cohort's percentile) were excluded. Because of this exclusion criterion, dietary data were available for 7,277 women born between 1925 and 1930.

Socioeconomic and lifestyle backgrounds have been associated with hormone use (39-42). We constructed several variables pertaining to these factors, using data from the questionnaire completed closest to the time that the dietary questionnaire was completed. These variables included sociodemographic characteristics

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(age, marital status education level) and some behavioral factors (body mass index in kg/m^2 (<18.5, 18.5-24.9, 25-29.9, ≥30), average alcohol consumption in g/day (0, 0.1-10, 10.1-20, >20), dietary energy intake in kcal/day (≤1500, 1501-1900, 1901-2300, >2300), average time spent in leisure physical activity in minutes/day (<15, 15-29.1, 30-44.9, ≥45) and participation status in the cohort study (a dichotomous variable equal to 'yes' if all study questionnaires preceding the dietary questionnaire were returned). Other variables related to gynecological follow-up (ever had a mammography, ever had a Papanicolaou smear, past use of oral contraceptives) as well as personal gynecological history (type of menopause, age at menopause, history of menopausal symptoms). Our analysis also considered history of vascular disease (myocardial infarction, angina pectoris or stroke), at least one cardiovascular risk factor (hypertension, diabetes mellitus or hypercholesterolemia), and "osteoporosis history" (ever use of a non-hormonal osteoporosis treatment or personal/maternal history of hip fracture).

We excluded from the analysis two women who declared never having menstruated (atypical hormonal profile) and 578 who reported a cervical, endometrial, ovarian or breast cancer (HRT contraindication). Finally, the analysis included data relating to 6,697 women with physiologically plausible dietary data and no categorical HRT contraindication.

Age at HRT initiation was missing for 239 ever users. These women were excluded from the analyses if this information was necessary (in particular, to contrast the early users from the treatment delayers among HRT users). Missing values for covariates were replaced by the modal value when 5 percent or less of the values were missing (marital status: 5 percent, education level: 4 percent, leisure physical activity: 2 percent). We systematically checked that results were unchanged when subjects for whom one or more values for any variable were missing were excluded from the analyses

Statistical analysis

We performed kernel density estimation (43) to illustrate the different patterns of HRT use among ever users, resulting in the differentiation between early users (HRT initiation within 3 years of menopause; n = 1,285) and treatment delayers (later initiation, n = 1,153). These two groups of women who ever used HRT were compared with those who never did (n = 4,020) by using logistic regression. In this paper, associations are given as odds ratios together with 95 percent confidence intervals.

We compared the associations between HRT use and non-dietary factors in our data with results from previous studies. This preliminary analysis pointed out the risk of confounding bias when studying the HRT-nutrition associations. All the variables studied in that first step were then included as potential confounders in the multivariate models assessing nutritional factors. Daily nutritional intakes of macronutrients (e.g., carbohydrates, proteins), micronutrients (e.g., vitamins and minerals) and food groups (e.g., fish , eggs, meat) were trichotomized according to the tertile distributions among all subjects. The macronutrients and micronutrients were entered singly into separate multivariate logistic regression models, and the food-group intakes variables were entered simultaneously. Tests for linear trend were performed by using the ordinal score on categories of each nutritional intake.

Because associations between nutritional variables and HRT use may vary according to some individual characteristics, we checked for interactions by entering multiplicative "intake X covariable" terms into separate multivariate models for each nutrient. If an interaction term was statistically significant we conducted stratification analyses on subpopulations according to the covariate.

Except for the kernel density estimation which was computed with R software, version 2.3.0 (Internet address: http://www.r-project.org, (44)), all analyses were performed using the SAS software, version 9.1 (SAS Institute, Inc., Cary, North Carolina). All results were considered significant at the 5 percent level. All statistical tests were two-sided.

RESULTS

Of the 6,697 women in the sample, 2,677 (40 percent) reported HRT ever use. Age at HRT initiation was bimodal with a first peak at about age 50 years and a second peak at approximately 60 years (figure 1). This bimodality was observed for women born in 1925-1927 as well as for women born in 1928-1930. The cutpoints for the first, second and third quartiles of treatment duration (truncated for half the women who currently used HRT at the time they completed the dietary questionnaire) were 1.2, 3.3 and 7.6 years, respectively. The cutpoints for the first, second and third quartiles of delay between menopause and HRT initiation were 0, 3 and 9 years respectively. In a complementary analysis (data not shown), we compare HRT early users (HRT initiation within 3 years of menopause: n = 1,285) with treatment delayers (later initiation; n = 1,153) regarding various characteristics to evaluate to what extent these two groups of HRT users differed. Little difference was seen except for covariates relating to the motivation of HRT initiation (type of menopause, age at menopause, osteoporosis history). Given the similarity in other variables, HRT delayers and early users were considered together as “HRT ever users” and compared with “never users” in subsequent analyses.

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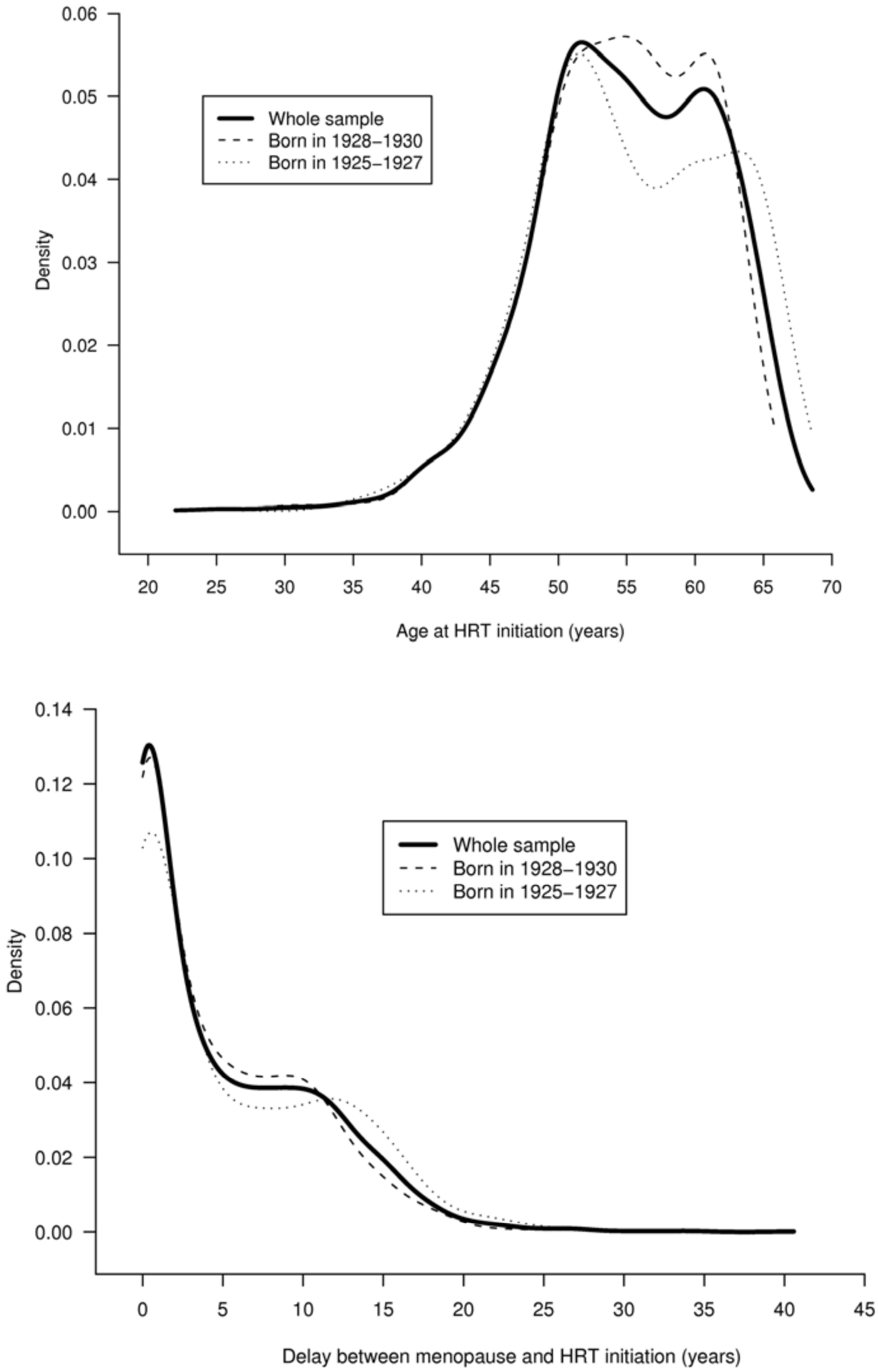
FIGURE 1. **Patterns of hormone replacement therapy (HRT) use by ever users: kernel density estimation of age at HRT initiation (top) and of the delay between menopause and HRT initiation (bottom) for the strata of women born in 1925-1930, E3N study, France, 1990-1995**



HRT early users and treatment delayers were compared with never users regarding sociodemographic, behavioral, and health characteristics (table 1) adjusting for personal gynecological history.

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TABLE 1. **Comparison of HRT* ever users (*n* = 2,677) with never users (*n* = 4,020) regarding some sociodemographic, behavioral, and medical variables† using a multivariate logistic regression model‡ for the strata of women born in 1925-1930, E3N Study, France, 1990-1995**

	Never users	Ever users	Probability of HRT ever use	
			OR*	95% CI*
Mean age in years (standard deviation) at completion of the dietary questionnaire	65.7 (1.8)	65.3(1.7)	0.94	0.91, 0.97
Marital status				
Married or with partner	74.3	79.0	1	
Single	25.7	21.0	0.84	0.74, 0.95
No. of years of education				
≤ 8	9.5	4.5	1	
9-11	10.0	9.0	1.79	1.36, 2.37
12-14	55.9	54.7	1.96	1.55, 2.46
15-16	11.3	13.8	2.36	1.81, 3.07
≥ 17	13.3	17.9	2.70	2.09, 3.50
Body mass index (kg/m^2)				
<18.5	3.1	2.7	0.93	0.68, 1.28
18.5-24.9	62.9	71.7	1	
25-29.9	27.2	22.2	0.75	0.67, 0.86
≥30	6.8	3.4	0.54	0.42, 0.70
Alcohol consumption (g/day)				
0	7.5	5.0	0.76	0.60, 0.95
0.1-10	57.0	55.1	1	
10.1-20	18.7	20.9	1.13	0.98, 1.30
>20	16.8	18.9	1.10	0.95, 1.27
Dietary energy intake§ (kcal/day)				
≤1500	21.5	17.0	0.81	0.69, 0.95
1501-1900	29.6	30.7	1	
1901-2300	24.8	27.9	1.06	0.92, 1.22
>2300	24.1	24.4	0.96	0.84, 1.11
Leisure physical activity (min/day)				
<15	21.5	17.7	1	
15-29.1	32.8	33.1	1.12	0.96, 1.30
30-44.9	20.0	20.9	1.09	0.92, 1.30
≥45	25.6	28.4	1.16	0.99, 1.36
Compliance in the cohort study¶				
No	4.9	1.9	1	
Yes	95.1	98.1	2.23	1.60, 3.11
Mammogram				
Never	27.8	8.1	1	
Ever	72.2	91.9	3.71	3.15, 4.37
Papanicolaou smear				
Never	12.5	4.0	1	
Ever	87.5	96.0	2.15	1.70, 2.73
Past use of oral contraceptives				
No	86.3	74.5	1	
Yes	13.7	25.5	1.98	1.73, 2.26
History of vascular disease#				
No	95.3	96.5	1	
Yes	4.7	3.5	0.85	0.65, 1.13
Cardiovascular risk factors**				
No	50.9	54.4	1	
Yes	49.1	45.6	0.90	0.81, 1.01
History of osteoporosis††				
No	72.0	65.2	1	
Yes	28.0	34.8	1.27	1.13, 1.42

* HRT, hormone replacement therapy; OR, odds ratio; CI, confidence interval.
† All values except those in row 1 are percentages.
‡ Full model including simultaneously all variables listed above plus type of menopause (natural; artificial), age at menopause (≤45; 44.9-54.9; ≥55), and menopausal symptoms (never, ever).
§ Except energy from alcohol.
¶Dichotomous variable equal to ‘yes’ if each of the first three E3N Study questionnaires were returned.

History of myocardial infarction, angina pectoris, or stroke.
**History of hypertension, diabetes mellitus or hypercholesterolemia.
††Ever-use of a nonhormonal osteoporosis treatment or personal/maternal history of hip fracture.

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Compared with never users, HRT users were significantly younger. They were also more likely to live with a partner, to have a higher level of education, and to have completed the questionnaires in the cohort study. HRT users were also less likely to be overweight (BMI ≥ 25kg/m^2) and abstinent. Their energy intake (energy from alcohol not included) tended to be greater than 1,500 kcal per day. Moreover, HRT use was significantly associated with ever having a mammogram or a Papanicolaou smear, past use of oral contraceptives and a history of osteoporosis.

Table 2 provides basic statistics of dietary intakes of 28 macro- or micronutrients according to HRT use as well as results of multivariate logistic regression analyses. HRT users tended to have a significantly higher dietary intake of ω3 fatty acids, vitamin B6, vitamin B12, vitamin D, and phosphorus compared with never users. HRT users tended also had a lower intake of starch. There was little difference between early initiators and treatment delayers in the observed associations between HRT use and nutrient intakes (data not shown).

TABLE 2. **Comparison of HRT* users (*n* = 2,677) with never users (*n* = 4,020) by tertiles of daily dietary nutrient intake using multivariate logistic regression analysis† for the strata of women born in 1925-1930, E3N Study, France, 1990-1995**

Daily nutrient intake	Mean (standard deviation)		Probability of HRT ever use				
			Tertile 2 vs. Tertile 1		Tertile 3 vs. Tertile 1		
	Never users	Ever users	OR*	95% CI*	OR*	95% CI*	*p* for trend‡
Total carbohydrates (g)	225.4 (76.3)	227.6 (71.8)	1.00	0.85, 1.18	0.96	0.77, 1.19	0.702
Simple carbohydrates (g)	106.2 (39.7)	109.0 (39.4)	0.99	0.86, 1.14	1.12	0.95, 1.32	0.175
Starch (g)	119.2 (54.2)	118.6 (49.8)	0.99	0.86, 1.15	0.79	0.66, 0.94	0.006
Dietary fiber (g)	24.3 (8.1)	24.8 (8.0)	1.06	0.91, 1.22	1.05	0.88, 1.24	0.617
Proteins (g)	86.2 (25.9)	88.6 (24.1)	1.16	1.00, 1.36	1.19	0.98, 1.46	0.083
Total lipids (g)	80.0 (26.7)	81.5 (25.2)	1.04	0.89, 1.21	1.15	0.94, 1.39	0.169
Saturated fatty acids (g)	31.8 (12.5)	32.3 (11.7)	1.12	0.97, 1.30	1.03	0.86, 1.23	0.746
Monounsaturated fatty acids (g)	28.0 (10.0)	28.7 (9.4)	1.13	0.98, 1.31	1.18	0.99, 1.41	0.063
Polyunsaturated fatty acids (g)	13.8 (6.1)	14.0 (5.9)	1.02	0.89, 1.17	0.97	0.84, 1.13	0.690
ω6 fatty acids (g)	12.4 (5.8)	12.5 (5.6)	1.06	0.93, 1.22	0.96	0.83, 1.11	0.597
ω3 fatty acids (g)	1.4 (0.6)	1.4 (0.6)	1.09	0.94, 1.25	1.23	1.05, 1.44	0.008
Vitamin A§(µg retinol equiv.)	1,760 (1,146)	1,773 (1,112)	0.94	0.82, 1.07	1.04	0.90, 1.19	0.578
Beta-carotene (µg)	4,125 (1,818)	4,215 (1,737)	1.09	0.96, 1.25	1.06	0.93, 1.21	0.403
Retinol (µg)	1,073 (1,089)	1,070 (1,046)	1.06	0.93, 1.22	1.06	0.93, 1.22	0.382
Vitamin B1 (mg)	1.2 (0.4)	1.3 (0.4)	1.02	0.87, 1.18	1.14	0.94, 1.37	0.170
Vitamin B2 (mg)	2.1 (0.7)	2.2 (0.7)	1.05	0.91, 1.20	1.11	0.95, 1.30	0.192
Vitamin B3 (mg)	21.8 (8.6)	22.1 (8.3)	1.00	0.87, 1.14	1.05	0.91, 1.22	0.473
Vitamin B5 (mg)	5.4 (1.7)	5.5 (1.6)	1.02	0.88, 1.18	1.18	0.99, 1.41	0.060
Vitamin B6 (mg)	1.7 (0.5)	1.8 (0.5)	1.14	0.98, 1.32	1.33	1.11, 1.59	0.002
Vitamin B9 (µg)	397.1 (120.6)	402.1 (116.1)	1.04	0.90, 1.19	0.94	0.80, 1.10	0.424
Vitamin B12 (µg)	7.6 (4.9)	7.9 (4.7)	1.16	1.01, 1.32	1.36	1.18, 1.57	0.000
Vitamin C (mg)	142.0 (64.8)	145.3 (61.5)	1.17	1.03, 1.34	1.11	0.97, 1.28	0.146
Vitamin D (µg)	2.4 (1.3)	2.5 (1.4)	1.06	0.93, 1.21	1.16	1.01, 1.34	0.032
Vitamin E (mg)	13.5 (5.9)	13.6 (5.7)	1.04	0.91, 1.19	0.97	0.84, 1.12	0.625
Calcium (mg)	1,014 (424)	1,037 (404)	1.30	1.14, 1.50	1.17	1.00, 1.36	0.056
Iron (mg)	13.2 (3.8)	13.5 (3.7)	1.05	0.90, 1.23	1.06	0.87, 1.28	0.579
Magnesium (mg)	391.0 (128.5)	395.1 (124.3)	0.90	0.78, 1.03	1.02	0.87, 1.19	0.775
Phosphorus (mg)	1,338.4 (423.7)	1,374.1 (404.5)	1.26	1.08, 1.47	1.26	1.04, 1.52	0.021

* HRT, hormone replacement therapy; OR, odds ratio; CI, confidence interval.

† Nutrient intake introduced one by one in the model. Adjustment for type of menopause, age at menopause, menopausal symptoms and all the other variables listed in table 1.

‡ Test for linear trend using ordinal score on tertile categories.

§ Vitamin A = Retinol + 1/6 Beta-carotene.

These differential nutrient intakes are related to different eating patterns, as shown in table 3, which compares HRT users with never users regarding consumption of 18 food-groups. HRT users ate significantly more fish, potatoes, milk and yogurt. They drank more alcoholic drinks as well as more coffee and tea. Compared with nonusers, HRT users also tended to eat fewer eggs, dried vegetables and cereals products.

Four covariables appeared to significantly interfere in one or more associations between nutrient intake and HRT use (*p* for interaction < 0.05): age, body mass index, leisure physical activity and cardiovascular risk factors. However, stratification analyses on subpopulations according to these variables revealed no significant inverse trend concerning nutrient-HRT associations.

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TABLE 3. **Comparison of HRT* users (*n* = 2,677) with never users (*n* = 4,020) by eating habits using a multivariate logistic regression model† for the strata of women born in 1925-1930, E3N Study, France, 1990-1995**

Daily food-group intake (g/day)	Mean (standard deviation)		Probability of HRT ever use				
			Tertile 2 vs. Tertile 1		Tertile 3 vs. Tertile 1		
	Never users	Ever users	OR*	95% CI*	OR	95% CI	p for trend‡
Potatoes	64.6 (56.8)	66.8 (54.7)	1.11	0.97, 1.27	1.20	1.04, 1.39	0.010
Vegetables	274.2 (135.0)	279.2 (127.2)	1.11	0.96, 1.28	0.91	0.77, 1.08	0.260
Dried Vegetables	15.0 (21.0)	14.7 (20.5)	0.99	0.87, 1.13	0.85	0.74, 0.98	0.042
Fruits & fruit juice	350.5 (208.7)	352.3 (198.0)	0.92	0.81, 1.06	0.92	0.80, 1.06	0.238
Milk & yoghurt	230.6 (198.6)	242.3 (195.9)	1.17	1.02, 1.33	1.25	1.08, 1.44	0.002
Cheese	50.3 (40.9)	49.6 (37.3)	0.97	0.85, 1.11	0.96	0.84, 1.11	0.722
Cereal products§	193.6 (104.5)	192.4 (96.8)	0.95	0.82, 1.09	0.80	0.68, 0.95	0.016
Meat	91.5 (54.1)	95.8 (51.9)	1.05	0.92, 1.20	1.11	0.96, 1.28	0.135
Fish	36.2 (28.5)	40.3 (29.9)	1.25	1.09, 1.43	1.32	1.15, 1.52	0.000
Eggs	24.1 (23.3)	22.4 (21.5)	1.05	0.92, 1.19	0.83	0.72, 0.96	0.010
Vegetable fats	8.6 (6.5)	9.1 (6.6)	0.98	0.85, 1.13	1.14	0.98, 1.33	0.090
Animal fats	9.5 (10.2)	9.7 (9.9)	1.12	0.98, 1.29	1.06	0.92, 1.23	0.278
Refined products¶	88.1 (65.3)	92.5 (66.3)	0.95	0.83, 1.09	0.99	0.85, 1.15	0.789
Sodas#	6.7 (32.7)	6.1 (29.9)	1.18	0.97, 1.44	0.92	0.74, 1.16	0.757
Tea & coffee	418.9 (301.4)	439.8 (300.9)	1.05	0.92, 1.20	1.15	1.01, 1.32	0.041
Alcoholic drinks	115.2 (158.9)	124.3 (153.3)	1.19	1.04, 1.36	1.21	1.06, 1.39	0.005
Spices & sauce	21.7 (12.7)	21.9 (12.2)	1.12	0.98, 1.29	1.06	0.91, 1.24	0.425
Soups	150.0 (127.0)	151.0 (124.5)	1.08	0.94, 1.23	1.03	0.90, 1.18	0.429

* HRT, hormone replacement therapy; OR, odds ratio; CI, confidence interval.
† Full model including simultaneously all 18 daily food group intakes listed above. Adjustment for type of menopause, age at menopause, menopausal symptoms and all of the other variables listed in table 1 (except 'alcohol consumption' to avoid a redundancy with 'alcoholic drinks').
‡ Test for linear trend using ordinal score on categories.
§ Bread, pasta and rice.
¶ Sugar, confectionary, dessert, cakes & biscuits.
# Because of the high percentage of non consumers, it was not possible to obtain balanced tertiles for this variable. The population was therefore split into groups: nonconsumption (86.2%), consumption of <20g/day (7.3%), consumption of ≥20g/day (6.5%).

DISCUSSION

In this study that was restricted to women born between 1925 and 1930, several characteristics were significantly associated with HRT use. We found, in agreement with many studies (23, 24, 45-55), that HRT use was associated with a higher level of education, a lower body mass index and a regular gynecological follow-up. This healthy HRT user effect is multidimensional since several types of selection may play a part. Among the observed HRT covariates in our study, dietary factors that have been linked both with cardiovascular and/or cognitive health occupied a notable place.

Few studies have examined the nutritional aspect of the healthy HRT user effect. Concerning dietary factors, the most studied and consistent association relates to alcohol consumption: HRT users tended to have a higher (but still moderate) alcohol intake than nonusers (23, 42, 45, 46, 50). Since women who drink moderately have a better cardiovascular risk profile (56), this result is consistent with the idea of a healthy HRT user bias. In fact, light or moderate drinking may be a sign of good health, while not drinking at all may reflect poor underlying health. HRT use was also found to be positively related to fat index and fiber index (24), to the healthy diet factor score (57) and to vegetable intake (45). Moreover, some authors found a positive association between HRT use and supplement consumption (45, 46, 49).

However to the best of our knowledge, there has been so far no study devoted to exploring the HRT-diet relation. The French National Education System Study cohort provided an excellent setting for examining this topic. Adjusting for health and lifestyle characteristics, we found in our population of elderly women, that HRT ever users, compared with never users, had significantly higher intakes of alcohol, ω3-fatty acids, vitamin B6, vitamin B12, vitamin D, and phosphorus and a lower intake of starch. These differential nutrient intakes were related to differences in eating habits. In particular, HRT users (whatever the stratum or the timing of HRT initiation) ate more fish than nonusers did. Particularly noteworthy is the fact that most of

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these nutritional variables have been associated with a lower risk of both cardiovascular disease and cognitive impairment. For example, homocystein metabolism has been evidenced as a potential risk factor for dementia and cardiovascular disease (58, 59). Similarly, fish consumption (as well as ω3-fatty acid intake) was shown to be associated with reduced dementia (60, 61).

Nontheless, our results are not completely consistent with the hypothesis of an healthy HRT user effect. For example, HRT use was found to be significantly associated with higher potatoes intake whereas no association with higher consumption of vegetables or fruits (largely considered an important component of a healthy dietary pattern) appeared in our sample. Such consideration weakens the argument that observational studies showing inverse relationships between HRT and heart disease were confounded by dietary factors. On the other hand, the nutrient approach remained quite consistent with the idea of an healthy user effect, adding further support to the risk of dietary confounding when studying HRT effect.

However, our findings cannot be directly extrapolated to other populations because they are based on a national French sample restricted to members of the national health insurance plan for teachers and coworkers, who volunteered to participate in medical research. Moreover, our results are based on data obtained during the 1990s, when HRT was promoted not only against menopausal symptoms but also to prevent chronic diseases such as osteoporosis (62). Given the recent changes in recommendations for hormone use limited to symptom control around the time of menopause (63, 64), the associations may be somewhat different today and have to be tested in other populations.

In addition, no data on women's attitudes toward HRT (representations of menopause, beauty care etc.) and on the influence of health care professionals (e.g., discussion with physicians, encouragement/discouragement to use HRT) were available, compelling us to discuss cautiously the direction of causality of the observed statistical associations. Finally, our analyses point to the need to consider as potential confounders many variables including dietary factors when investigating in observational studies the association between HRT use and outcomes such as cardiovascular disease or dementia. Indeed, we found in our population that HRT use was consistently associated with some nutritional intakes. Since nutrition relates strongly to health (in the elderly specifically (65, 66)), confounding bias may affect results when overlooking the nutritional status in observational designs.

To date, nutritional status is not known to have not been taken into account in large observational studies of HRT use and cardiovascular disease or dementia. This omission could partly explain the intriguing discrepancies between these studies and randomized controlled trials, since some nutrient intakes may differ according to HRT use. Epidemiologists have to keep in mind that the healthy HRT user effect can encompass higher socioeconomic status, healthier lifestyle and better medical follow-up but also differential nutrient intakes ensuing from differential dietary preferences.

Acknowledgment

The E3N study is supported by the French League against Cancer, the European Community, the 3M Company, the "Mutuelle Générale de l'Education Nationale", the French Institute of Health and Medical Research, the Gustave Roussy Institute and several General Councils in France. M.-N. Vercambre was given a grant from Statlife and the "Association Nationale de la Recherche Technique". None of the funding agencies played a role in the design and conduct of the study, analysis and interpretation of the data, or preparation and approval of the manuscript.

The authors are grateful to L. Hoang, M. Niravong, and M. Fangon for their technical assistance; to M. Touillaud and D. Delanoë for their fruitful discussions; to all members of the E3N group; and to Johanna Norton for her assistance with the English language.

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