A prospective study of hormone therapy and depression in community-dwelling elderly women: the three city study.

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Journal of Clinical Psychiatry, in press
Abstract: 244 words
Text: 3627 words
Number of Tables: 4

A prospective study of hormone therapy and depression in community-dwelling elderly women (The Three City Study)

Running title: Hormone therapy and late-life depression

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Acknowledgements and conflict of interest declaration
All authors report no competing interests. The 3C Study is conducted under a partnership agreement between Inserm, the Victor Segalen – Bordeaux II University and Sanofi-Synthélabo. The Fondation pour la Recherche Médicale funded the preparation and first phase of the study. The 3C-Study is also supported by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, Institut de la Longévité, Agence Française de Sécurité Sanitaire des Produits de Santé, the Regional Governments of Aquitaine, Bourgogne and Languedoc-Roussillon and, the Fondation de France, the Ministry of Research-Inserm Programme "Cohorts and collection of biological material". Part of this project is financed by a grant from the Agence Nationale de la Recherche (ANR) project 07 LVIE 004.

ABSTRACT

Background: The potential benefits of hormone therapy in treating depressed postmenopausal women are controversial and data on depression (re)emergence in the context of HT discontinuation are lacking.

Objective: To determine whether hormone therapy is associated with a modified risk of new onset of depressive symptoms in elderly women.

Method: Current depressive symptomatology was evaluated in 4069 community-dwelling postmenopausal women aged 65 years and over, randomly recruited from three French cities. Depressive symptomatology was assessed using the Centre for Epidemiologic Studies Depression Scale at baseline and as part of the 2- and 4-year follow-up.

Results: Over the follow-up period, multivariate logistic regression analyses adjusted for socio-demographic variables, measures of physical health and cognitive impairment, failed to find a significant association between HT at baseline and the incidence of depressive symptoms. However further analysis indicated an increased risk of incident depressive symptoms for women using specifically transdermal estradiol treatment combined with synthetic progestin (OR=1.59, 95%CI 1.01-2.50, p=0.046). In addition, while women taking hormone therapy continuously over the 4-year follow-up did not show an increased risk of depressive symptoms, women who stopped their treatment early after inclusion, had a significantly higher risk (OR= 2.63 95%CI 1.52-4.55, p=0.0005).

Conclusion: Hormone therapy was not associated with a protective effect against the emergence of depressive symptoms in elderly postmenopausal women however discontinuing treatment could increase the risk of depressive symptoms. Data on the appropriate management of depression in the context of hormone therapy discontinuation among postmenopausal women requires further investigation.

KEY WORDS: Depression, estradiol, postmenopausal, progestogen, transdermal

INTRODUCTION

Although the neuroprotective effects of estrogen have been demonstrated experimentally, the benefits of hormone therapy (HT) in treating depressed menopausal women remain controversial (see for review[1]). Recent trials in women with clinically diagnosed depression, report a positive effect of short-term transdermal estrogen therapy in perimenopausal women,[2, 3] with the antidepressant response in depressed postmenopausal women being much weaker.[4, 5] However, no trials have evaluated the effect of different treatment regimens on depressed elderly women, especially those containing progestogen, which could decrease estrogen's antidepressant effect,[6-8] or the impact of long-term use. A history of psychiatric disorder or other individual characteristics could also influence the response to HT, as well as the decision to start or discontinue treatment. Nevertheless, data on depression (re)emergence after HT discontinuation are lacking, especially following the results of the much publicized Women's Health Initiative (WHI) study in 2002[9] which has led to a worldwide decrease in HT prescription. While differences in vulnerability to psychiatric disorders and the role played by HT remains an important question to be addressed, it is however, unlikely to be answered in the near future by large-scale randomized-controlled trials (RCTs) with long-term HT users. On the other hand, it is currently feasible to use existing data from large-scale longitudinal population-based studies with adequate information on hormone exposure and psychiatric evaluation. The present study aimed to determine whether HT could be associated with a lower incidence of depressive symptomatology in a large population-based cohort of postmenopausal women. The impact of HT discontinuation on depressive symptoms was also evaluated. In this study we controlled for socio-demographic variables, measures of physical health including insomnia, as well as cognitive impairment, which may independently contribute to both depression and HT prescription. We also took into account the history of depression as well as the type of HT used.

METHOD

Study population

The data used for this analysis were derived from a general population study of neuropsychiatric disorders in community-dwelling French elderly (3C Study). Eligible participants, who were at least 65 years of age and non-institutionalized, were recruited from the electoral rolls of three French cities (Bordeaux, Dijon, Montpellier) between 1999 and 2001. The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre. After obtaining written informed consent from all participants, interviews were administered by trained staff at baseline and every two years thereafter. The 3C study has been described in further detail elsewhere.[10]

Outcome measures

The Centre for Epidemiologic Studies Depression Scale (CESD) is a 20-point questionnaire designed to measure current depressive symptoms in the general population which has been validated in the elderly.[11] It has been suggested that a cutoff point of 23 or more can be used to identify major depressive disorder (MDD).[12] The diagnosis of lifetime psychiatric disorders was made using the Mini-International Neuropsychiatry Interview (MINI), a standardized psychiatric examination which has been validated in the general population[13] according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria.[14]

Women scoring 23 or over or those taking antidepressants were considered as having current depressive symptomatology in this analysis. Incident cases of depressive symptoms were identified from subjects who had neither depressive symptoms (CESD<23), nor were using antidepressants at baseline, but who subsequently presented with high depressive symptomatology or reported antidepressant treatment during at least one of the two follow-up examinations.

Hormone therapy and menopausal characteristics

All types of medication used during the preceding month (including HT and antidepressants) were validated by presentation of the prescription or the medication itself. Information was also recorded on past HT type, time of initiation, and duration of use, as well as age at menopause (defined as one year without menses) and type of menopause (*i.e.* natural *vs.* surgical or following a treatment such as chemotherapy or radiotherapy).

Socio-demographic and clinical variables

The standardized interview included questions on demographic characteristics, education level, height and weight. Information was obtained on type and quantity of alcohol consumption (number of g of alcohol per day) and tobacco use. Participants were classified as disabled if they were unable to complete at least one task from either the Instrumental Activities of Daily Living (IADL)[15] or the Activities of Daily Living (ADL)[16] scales. Cognitive function was assessed using the Mini-Mental State Examination (MMSE)[17] and those scoring less than 26 were classified as cognitively impaired. Women were questioned about their sleeping habits and insomnia was defined as scoring positive on at least two questions from the 5-item sleep subscale of the Nottingham Health Profile questionnaire.[18] Blood pressure was measured during the interview using a digital electronic tensiometer OMRON M4. Detailed medical questionnaires (with additional information where necessary from general practitioners) were used to obtain information on history of vascular diseases, including ischemic pathologies (*e.g.* angina pectoris, myocardial infarction, stroke, cardiovascular surgery), non-ischemic pathologies (*e.g.* bradycardia or palpitations), and other chronic illnesses, *e.g.* asthma, diabetes (fasting glucose≥7.0mmol/l or reported treatment), hypercholesterolemia (total cholesterol ≥6.2mmol/l), hypertension (resting blood pressure ≥160/95mm Hg or treated) and thyroid problems. Participants were classified as having a chronic health disorder if they suffered from one or more of these illnesses.

Statistical Analysis

Two-tailed chi-squared tests were used to compare categorical variables and t-tests and ANOVA for continuous variables. For subsequent subgroup comparisons, Bonferroni adjustment for multiple comparisons was used. Among all the socio-demographic or health variables recorded, those which were found to be associated with depressive symptoms at the 15% significance level ($p<0.15$), were considered in the multivariate analysis. In the final models we thus adjusted for centre, age (continuous), education level (≥12 years of schooling), widowhood, cognitive impairment, insomnia, history of chronic disorders, disability, age at menopause (continuous), and past depression. For the variables which were treated as continuous the linearity assumption was checked. In longitudinal analysis we used multi-adjusted logistic regression models to evaluate the predictive value of HT taken at baseline on new-onset depressive symptoms over 4-year follow-up. We also evaluated these risks for women who have taken HT continuously, or those who have stopped during the 4-year follow-up compared to never users, using the multi-adjusted models (see above). SAS version 9.1 (SAS Institute, Inc., North Carolina) was used for the statistical analysis with a significance level of $p<0.05$.

RESULTS

Population characteristics as a function of HT use

Of the women recruited as part of the 3C Study (n=5644), only non-demented women (diagnosed using DSM-IV revised criteria[19]), with complete follow-up data, who were assessed for depressive symptomatology, who had information relating to the use of HT and had no missing data for the main covariates considered in the multivariate logistic models (n=4069), were included in this analysis. Women not included in this analysis had a lower educational level, were older, more likely to have disabilities and cognitive dysfunction ($p<0.001$) and were more

frequently widowed (p=0.002). They were also more likely to have lifetime depression and use antidepressants (p<0.01) and less likely to use or have used HT (p<0.0001). There were no significant differences regarding the other variables between the excluded subjects and those included in this analysis.

The 4069 women included in the present analysis had a mean (SD) age of 73.6 (5.0), ranging from 65 to 93 years. In our sample, 14.7% currently used HT and 19.9% reported past use. The median (min, max) duration of past HT use was 5 years (1-39) and 12 (1-43) for current users. Transdermal estradiol was used by the majority of current HT users (78.6%) either unopposed (16.9%) or combined with oral progesterone (29.9%) or synthetic progestin (31.8%). Oral estradiol was used by only 18.0% of women, with 2.0% using unopposed, 3.6% combined with progesterone and 12.4% with synthetic progestin. None of these French women used other estrogen derivatives, such as ethinylestradiol, or conjugated equine estradiol (CEE), however a small proportion (3.3% overall) were prescribed other forms of HT (for example tibolone or cyproterone, or progestogen alone).

Current, past and never HT users differed significantly on most socio-demographic and clinical characteristics except tobacco consumption, current antidepressant use, hypercholesterolemia, and asthma **(Table 1)**. Never users were significantly older, more frequently widowed, and more frequently reported natural menopause than ever (current or past) users. Never and past users did not differ significantly regarding the other health variables (including the vascular ones). On the other hand, current users of HT appeared different to both past and never users. They were younger, less frequently widowed, had significantly higher education levels, a higher age at menopause and lower BMI. They were also less likely to have physical disabilities, cognitive impairment, insomnia, chronic disorders (*e.g.* ischemic or non-ischemic pathologies, diabetes, high blood pressure) and breast cancer. Current users were more frequently alcohol consumers, had used HT later and for a longer period than past users, and were more likely to have thyroid dysfunction.

Population characteristics as a function of depressive symptoms

At baseline, 21.9% of women were identified as having depressive symptoms (CESD ≥23) or were currently using antidepressant. Depressed women were older, more frequently widowed, and with a higher percentage of physical or cognitive impairments, insomnia and past major depression (**Table 2**). They also reported a lower age at menopause. Among the women who were not depressed at baseline (CES-D<23 and not using antidepressants), 17.4% were identified as having depressive symptoms over the 4-year follow-up period. Women who developed new onset of depressive symptoms were older and with a higher percentage of disability, insomnia, and past major depression than women without depressive symptoms. Compared to women having baseline depressive symptoms they were however less frequently widowed and with a lower percentage of physical or cognitive impairment, insomnia, or past depression and reported a higher age at menopause.

Associations between current HT and incident depressive symptoms

The effect of current HT on incident depressive symptoms was evaluated longitudinally during follow-up after controlling for a large number of covariates, *e.g.* age, education level, center, widowhood, age of menopause, insomnia, physical disabilities, cognitive impairment, chronic disorders and past depression (**Table 3**). Overall, there was no significant adjusted association between baseline HT use and new-onset depressive symptoms (p=0.06). HT duration was not significantly associated with depressive symptoms (p=0.78, data not shown). However examining further the type of treatment used, opposed transdermal HT was associated with the incidence of depressive symptomatology; the effect of which appeared specifically related to the presence of synthetic progestin (OR=1.59, 95%CI 1.01-2.50). Other HT types, such as unopposed transdermal estrogen treatment or opposed oral treatment, were not significantly associated with a

modified risk of depressive symptoms. No significant associations were found with unopposed oral HT either, although in this case, the low numbers precluded the drawing of definite conclusions.

Among HT users without depressive symptoms at baseline, 34.5% of women continuously took HT during the 4-year follow-up and 65.5% ceased treatment; 16.2% stopped early in the follow-up, between inclusion and the first two-year follow up, and 49.3% stopped between the first and the second two-year follow-up. Only five women started a treatment after inclusion. Among all the socio-demographic and health variables examined, early discontinuing women only differed from those having continuously used HT by a higher BMI (48.0% vs. 32.10%, p=0.02). They notably did not differ significantly regarding HT type (p=0.86) or insomnia (p=0.28).

In fully adjusted models, we found no significant association between the continuous use of HT and new-onset depressive symptoms **(Table 4)**. The results were the same regardless of the type of HT used (data not shown), however with such small numbers in each of the sub-groups, this could likely result from a lack of statistical power. On the other hand, women having stopped their treatment early after inclusion, were at significantly increased risk of new-onset depressive symptomatology (OR=2.63, 95%CI 1.52-4.55).

DISCUSSION

HT and depressive symptoms in postmenopausal women

The present study indicates that current HT use was not significantly associated with a decreased risk of depressive symptoms in elderly postmenopausal women. Given the size of our sample, a power calculation indicates that the minimal difference in ORs which could have been detected is 30-40% (in absolute values). Since the median duration of current HT use was 12 years, our results are not compatible with the hypothesis that postmenopausal women require prolonged treatment to obtain a satisfactory antidepressant effect. This is also suggested by the

absence of significant association between HT duration and depressive symptoms. These results are consistent with previous clinical trials of short-term estradiol treatment, which primarily found a weaker association, if any, between treatment and depression in postmenopausal compared to perimenopausal women.[4, 5] This adds further weight to the hypothesis that there is a critical window of estrogen susceptibility limited to the perimenopausal period during which HT may have maximal antidepressant and neuroprotective effects.[20, 21]

Our results differ from that of a large cross-sectional study of 6602 postmenopausal women where a decreased risk of depressive symptoms was reported in current HT users.[22] In this study, 76% of the women were taking estrogen alone (mainly oral CEE) and a lower risk was observed in women using unopposed oral estrogen only, but not in combined HT users (estrogen combined with medroxyprogesterone acetate (MPA)). The small number of women currently using unopposed estrogen in our sample (especially for women using oral estrogen, n=9, of whom none used CEE) compared to those using opposed estradiol (80% of current users) could explain the inconsistencies. However, since we did not observe a protective effect with transdermal unopposed estradiol, one explanation could be related to differences in the depression measures used. Whooley et al. measured depressive symptoms using the short-form, self-report Geriatric Depression Scale[22] whereas we used the CESD, which covers a fuller range of depressive symptoms and has better criterion validity in the identification of MDD.[13, 23]

Interestingly, the results of our work do suggest that the effects of HT on depression in postmenopausal women may vary depending on the type of treatment used. CEE for example, is most commonly used in the United States but not necessarily elsewhere around the world,[24] which may help explain some inconsistencies in findings across studies. We also found that women who used transdermal estradiol associated with a synthetic progestin had an increased risk of depressive symptoms, while transdermal estradiol alone or in combination with natural progesterone was not significantly associated with the incidence of depressive symptoms. Although we could not definitively conclude to a specific deleterious effect of associated progestin

compared to progesterone, our data are supported by previous studies which have shown that the effects of HT on mood can be modified by changing the progestogens compound that is used. Synthetic progestin has been suggested to be an antagonist to estrogen and mitigate its mood-enhancing effect in postmenopausal women.[7, 8, 25] A negative effect on mood pattern was also reported in non-depressed postmenopausal women treated with progestogen in combination with estrogen, whereas no significant change or an improvement in mood was observed with estrogen alone.[26-29] Other studies however, reported no negative effect or even mood improvement.[30, 31] Although the results of our study do not suggest that the use of transdermal estradiol with synthetic progestin actually causes depressive symptoms, the presence of a significant associations warrants further investigation to help clarify the long-term effects of specific subtypes of progestins on depression.

Discontinuing HT and new-onset depressive symptoms in postmenopausal women

An intriguing finding from this study was the observed increased risk of new-onset depressive symptoms (OR=2.63 95%CI 1.52-4.55, p=0.0005) among women who stopped HT early on during the follow-up period, however there was no significant difference between continuous HT users and never users. This raises the question of why women stopped using HT. Examining group differences, past HT users at baseline differed from never users by being younger and less frequently widowed. Compared to current users, past users were older, less educated, more likely to be widowed and reported more frequently insomnia and a higher level of chronic disorders and disability, *i.e. a priori* at higher risk of depression. However, among current users at baseline, women who discontinued HT early after inclusion did not differ significantly from those having continuously used HT during the 4-year follow-up period, except for a higher BMI in the early discontinuing group. In addition, this association between discontinuing HT and the incidence of depressive symptoms persisted after adjustment for all potential confounders. In

our multiadjusted model, BMI was not considered as an adjustment variable since it was not significantly associated with depressive symptoms in univariate analysis (p=0.32). However, since continuing and early discontinuing women only differed by BMI among all the variables examined, we performed an additional multivariate model further adjusting for BMI; this did not modify the strength of the association and the same OR was observed (OR=2.66 95%CI 1.54-4.60, p=0.0005). Another possibility could be that discontinuation of HT increases the risk of depressive symptoms due to the (re)emergence of menopause-associated symptoms, particularly in those women who first initiated treatment for the control of menopause-associated depression. Vasomotor symptoms for example, have been independently associated with an increased risk of depression in peri-menopausal women[32] although this appears more unlikely in our older postmenopausal women who are on average 20 years post-menopause.[33] We also observed no difference regarding the frequency of insomnia between continuing and discontinuing women. Women with depressive symptoms may also be more likely to complain of menopausal symptoms and thus to be prescribed HT in the first place. We effectively observed that ever users of HT tended to have a more frequent history of past MDD, although controlling for a past history of depression did not modify the significance of the association. On the other hand, the risk was not significant for those having continued HT. Early or current stressful events have been reported to be associated with depression notably during the menopausal transition.[34] We have no information concerning specific stressful life events during the follow-up except bereavement; where there was no difference in the frequency of widows, between women who developed depressive symptoms during the follow-up period and those with no depressive symptoms. Hence, the underlying biological, neurochemical, or psychological mechanisms associated with re-emergence of depressive symptoms remains to be determined, but could include other processes altering the quality of life and overall functioning, *e.g.* increased proinflammatory activity or sexual dysfunction.[35]

An increase in mood disturbance among postmenopausal women due to declining

prescriptions of HT may thus be anticipated. Interestingly, Mc Intyre et al. reported that the decrease in the number of HT prescriptions following the WHI results in 2002, was associated with a statistically significant concomitant increase in prescriptions of serotonergic antidepressants, suggesting that antidepressants were being prescribed for symptoms (psychological, physical) previously controlled with the use of HT.[36] Data on the appropriate management of depression in the context of HT discontinuation are, however, lacking and require further investigation.[37, 38]

Limitations

This study has several limitations. Women taking antidepressants were classified as depressed, although it is possible that the treatment was prescribed for another psychiatric condition. This could have resulted in misclassification bias, however we have ensured that the findings were comparable if we considered only CESD scores and adjusted for antidepressant use in the analysis (data not shown). The data concerning some of the covariates were self-reported and may thus be subject to recall bias with depressed participants responding more negatively about their health. However, similar associations were seen in the unadjusted and adjusted analysis, thus suggesting that any bias did not have a substantial influence on the results. There is also the potential for bias in this analysis due to the exclusion of women with missing data. These women were older, with lower education level, more frequently widowed and with overall poorer health. In addition, there is prescription bias in regard to women who are given HT and we have shown that current users were significantly healthier than both past and never users. Therefore, despite controlling for a number of variables related to this, other factors which were not recorded, may have influenced the results.

Strengths

Despite these limitations, this study has a number of strengths. The data used in this analysis came from a large multicentre population-based prospective study of women aged 65 years and over and therefore the results are relevant to elderly women living in the community. Psychiatric evaluation was assessed by trained staff using a measure of depressive symptoms which has been validated in the elderly[11] and appears to be a good indicator of MDD.[12] The cohort design of this study allowed evaluation of long-term HT use and current HT use was verified at inclusion and at each follow-up by examining the prescriptions and medications themselves, thus minimizing exposure misclassification. We controlled for a large number of covariates linked to depression, thus minimizing any confounding, particularly measures of physical health (physical incapacities, chronic health conditions), insomnia and cognitive impairment. Finally, in contrast to the majority of community-based studies, we controlled for a history of past depression, which may confound the association between depressive symptoms and HT.

Conclusion

HT is still the first-line of treatment for the approximate 75% of women who experience menopausal symptoms and it remains an important therapeutic option for first episodes of mild and moderate depression occurring at the perimenopause, at least for women with no contraindications for estrogen treatment.[39] Older postmenopausal women, however, often stop HT after prolonged use and this discontinuation was dramatically exacerbated after the results of the WHI trial were published in July 2002.[9] It is, however, now generally acknowledged that the type of HT used in the WHI's RCT (CEE and MPA) could most likely result in a higher risk of adverse effects than natural HT formulations based on 17β-estradiol and progesterone.[24, 40] In fact, while much previous research has focused on whether all women should or should not use HT, our study suggests that practitioners may need to monitor more closely women who decide to discontinue

HT treatment, in particular with regard to breakthrough psychiatric symptoms and offer possible alternative treatments in the case of (re)emergence of depressive symptoms.[38, 41]

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Table 1. Baseline characteristics of participants according to HT use (n=4069).

Characteristic of HT users	**Never** (n=2662)	**Past** (n=808)	**Current** (n=599)	**p-value**[d]	**Significant 2x2 comparisons**
Centre:				<0.0001	Never vs. past or current, past vs. current
Bordeaux (%)	26.0	21.9	15.4		
Dijon (%)	50.7	50.7	59.8		
Montpellier (%)	23.3	27.4	24.9		
Age (Mean (SD))	74.5 (5.0)	73.1 (4.8)	70.3 (3.4)	<0.0001	Never vs. past or current, past vs. current
≥12 years of schooling (%)	33.3	33.4	45.6	<0.0001	Current vs. never or past
High current tobacco intake (> 5cigarettes/day) (%)	2.6	2.7	3.0	0.88	
Current high alcohol consumption (>24g/day) (%)	10.9	8.7	12.7	0.05	Past vs. current
Widowed (%)	38.9	32.7	20.9	<0.0001	Never vs. past or current, past vs. current
Disability[a] (%)	8.8	8.0	2.8	<0.0001	Current vs. never or past
Cognitive impairment [b] (%)	16.4	17.5	11.6	0.006	Current vs. never or past
Insomnia (%)	32.1	36.4	23.2	<0.0001	Current vs. never or past
Chronic disorders (%)	73.2	71.5	68.1	0.04	Current vs. never
- Ischemic cardiopathology	8.8	8.7	3.2	<0.0001	Current vs. never or past
- Stroke	3.4	3.0	1.5	0.03	Current vs. never or past
- Arteritis	2.5	1.9	1.4	0.20	
- Non ischemic pathologies (bradycardia, palpitations)	17.6	18.0	12.6	0.009	Current vs. never or past
- Thyroid dysfunction	11.3	11.8	16.8	0.001	Current vs. never or past
- Diabetes	6.4	5.5	2.2	0.0003	Current vs. never or past
- Hypertension	43.4	40.7	31.8	<0.0001	Current vs. never or past
- Asthma	7.7	8.4	9.1	0.47	
- Hypercholesterolemia	35.6	39.0	38.9	0.11	
Breast cancer	4.8	7.0	0.5	<0.0001	Current vs. never or past
Body Mass Index ≥ 25 kg/m^2 (%)	49.2	46.9	37.1	<0.0001	Current vs. never or past
Current depressive symptoms (CESD score ≥23) (%)	15.3	17.8	13.7	0.09	
Current antidepressant use (%)	9.7	9.9	9.0	0.97	
Past major depression[c] (%)	12.9	15.5	15.9	0.06	
Age at Menopause (Mean (SD))	49.4 (5.3)	48.3 (6.6)	50.1 (5.5)	<0.0001	Never vs. past or current, past vs. current
Type of Menopause				<0.0001	Never vs. past or current
Natural (%)	81.9	70.8	76.3		
Surgical (%)	6.0	12.5	9.6		
Other (i.e. treatment-related) (%)	12.2	16.7	14.1		
Age of HT initiation (Median (min-max))	---	50 (20-77)	56 (25-80)	<0.0001	Past vs. current
Duration of HT (Median (min-max)) for:	---	5 (1-39)	12 (1-43)	<0.0001	Past vs. current

[a]According to IADL and ADL criteria. [b]MMSE < 26. [c] According to the MINI. [d]Test-statistic were χ^2 or ANOVA for categorical or continuous variables, respectively. For subsequent subgroup comparisons, Bonferroni adjustment for multiple comparisons were used. Abbreviations: CESD= Centre for Epidemiology Studies Depression Scale, HT = Hormonal Therapy.

Table 2. Main baseline characteristics of participants according to the presence of depressive symptoms at baseline or follow-up.

Characteristic	**No depressive symptoms** (n=2104)	**Depressive symptoms at baseline** (n=714)	**New-onset depressive symptoms during follow-up** (n=443)	**p-value**
Centre:				0.05
Bordeaux (%)	24.43	23.25	23.48	
Dijon (%)	53.33	48.88	53.27	
Montpellier (%)	22.24	27.87	23.25	
Age (Mean (SD))	73.4 (5.0)	74.3 (4.9)	74.3 (5.2)	<0.0001
≥12 years of schooling (%)	36.8	33.1	33.7	0.15
Widowed (%)	33.5	41.9	35.2	0.0003
Disability (%)	5.0	14.6	9.3	<0.0001
Cognitive impairment (%)	12.6	22.4	18.1	<0.0001
Insomnia (%)	23.0	49.8	36.0	<0.0001
Chronic disorders (%)	71.3	74.7	73.1	0.20
Breast cancer (%)	3.9	4.8	2.7	0.35
Past major depression (%)	9.8	24.6	15.2	<0.0001
Age at Menopause (Mean (SD))	49.7 (5.3)	49.1 (5.3)	49.5 (5.7)	0.006

Same legend as in Table 1

Table 3. Adjusted models for the association between HT use and new-onset depressive symptoms after 4-year follow-up, among women without depression at baseline.

HT use at baseline[a] (n)	Depressive symptoms (%)	OR[b] [95% CI]	p-value
Never (2072)	17.13	1.0	
Current (470)	18.38	1.35 [1.00-1.83]	0.06
Never (n=2072)	17.13	1.0	
Unopposed transdermal (n=80)	16.25	1.06 [0.56-2.03]	0.85
Unopposed oral (n=9)	11.11	0.95 [0.11-7.85]	0.96
Opposed transdermal (n=292)	19.18	1.48 [1.03-2.12]	0.03
- *with progesterone (n=134)*	18.66	*1.36 [0.82-2.26]*	*0.24*
- *with synthetic progestin (n=158)*	19.62	*1.59 [1.01-2.50]*	*0.046*
Opposed oral (n=79)	20.25	1.47 [0.78-2.77]	0.23
- *with progesterone (n=13)*	23.08	*1.90 [0.51-7.07]*	*0.34*
- *with synthetic progestin (n=66)*	19.70	*1.38 [0.68-2.81]*	*0.37*
Other unrelated HT types (n=10)	nd	nd	nd

[a] Corresponds to opposed and unopposed estradiol-based HT. [b] Adjusted for age, educational level, centre, widowhood, age at menopause, insomnia, disability, cognitive impairment, chronic health disorders and history of depression.
Abbreviation: HT: Hormonal Therapy; nd: not determined.

Table 4. Adjusted models for the association between HT use after the inclusion and new-onset depressive symptoms after 4-year follow-up, among women without depression at baseline.

	HT use (n)	**Depressive symptoms (%)**	**OR[a] [95% CI]**	**p-value**
HT use 4-year after the inclusion	**Never** (n=2037)	15.95	1.0	
	Continuing (n=162)	17.90	1.34 [0.84-2.15]	0.22
	Discontinuing (early) [b] (n=76)	30.30	2.63 [1.52-4.55]	0.0005

[a] Adjusted for age, educational level, centre, widowhood, age at menopause, insomnia, disability, cognitive impairment, chronic health disorders and history of depression. [b] discontinuing between the inclusion and the first 2-year follow-up.
Abbreviation: HT = Hormonal Therapy.