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Inserm, U888, Montpellier, F-34093 France ; Univ Montpellier1, Montpellier, F-34000 France

*Corresponding Author: Joanne Ryan, Inserm U888, Nervous System Pathologies: Epidemiological and Clinical Research. Hôpital La Colombière, 39 av. Ch. Flahault, BP 34493, 34093 Montpellier Cedex 5, France. Email: ryan@montp.inserm.fr, Tel: +33 499 614 562, Fax: +33 499 614 579.

Received: 24 Aug 2007
Revision requested: 10 Oct 2007
Revised version received: 06 Nov 2007
Accepted: 14 Feb 2008

ABSTRACT

Background: Fluctuating hormone levels are known to influence a woman's mood and well-being. This study aimed to determine whether lifetime hormonal markers are associated with late-life depression symptoms among elderly community-dwelling women.

Method: Detailed reproductive histories of 1013 women aged 65 years and over were obtained using questionnaires and depressive symptoms were assessed using the Centre for Epidemiological Studies Depression Scale. Multivariate logistic regression models were generated to determine whether any lifetime endogenous or exogenous hormonal factors were associated with late-life depression.

Results: The prevalence of depressive symptoms was 17%. Age at menopause was associated with depressive symptoms, but only among women with a lower education level. For these women, an earlier age at menopause increased their risk of late-life depression (linear effect, OR=0.95, 95%CI: 0.91-0.99). The odds of late-life depression were also increased for women who were past (OR=1.6, 95%CI: 1.1-2.5), but not current hormonal replacement users. On the other hand, long-term oral contraceptive use (≥10 years) was protective against depression (OR=0.3, 95%CI: 0.1-0.9). These associations remained significant even after extensive adjustment for a range of potential confounding factors, including socio-demographic factors, mental and physical incapacities, antidepressant use and past depression. The other factors examined, including age at first menses, parity, age at childbirth and surgical menopause, were not associated with late-life depressive symptoms.

Conclusions: Lifetime hormonal factors that are significantly associated with depression symptoms in later life have been identified. Further work is needed to determine how potential hormonal interventions could be used in the treatment of late-life depression in certain sub-groups of women.

Key words: lifetime hormonal exposure, estrogen, depression, late-life

INTRODUCTION

Across the female lifespan, variations in hormonal levels and in particular that of the female sex hormone estrogen, have been linked to changes in mood and negative well-being (Steiner *et al.*, 2003). During the reproductive years, cyclic changes in the concentrations of ovarian hormones across the menstrual cycle can be accompanied by symptoms of irritability and depressed mood (Campagne and Campagne, 2007). During the last months of pregnancy or following childbirth the sudden change in hormone levels, notably estrogen, has been directly implicated in the development of depression (Bloch *et al.*, 2000). In the case of both premenstrual syndrome and postpartum depression, it has been suggested that this could affect only a subgroup of women, who show an abnormal response to hormonal fluctuations (Bloch *et al.*, 2000; Schmidt *et al.*, 1998). During the perimenopause, there are intense and irregular fluctuations in the levels of estrogen, which tend to decline up to the postmenopause, and this period appears to be associated with a higher risk of depressive symptoms (Bromberger *et al.*, 2007). A potential role for estrogen in depressed mood is further supported by the presence of estrogen receptors in the brain, and the finding that estrogen can modulate neurotransmitter activity (Andrade *et al.*, 2005). However, studies which have looked at the differences in serum hormone levels between depressed and non-depressed women, have been inconclusive. In some cases depressed women were found to have lower levels of estrogen (Harlow *et al.*, 2003; Young *et al.*, 2000), while in others, no differences were found (Erdincler *et al.*, 2004).

The benefits of hormone therapy (HT) in treating postmenopausal women with depressed mood is controversial, but this could be explained by differences in the duration and type of treatment used, for example estrogen versus combined estrogen-progesterone preparations, or oral versus transdermal preparations, and the age at which treatment is first started (*i.e.* peri- versus post-menopause) (see for review (Ancelin *et al.*, 2007)). In addition, while the potential link between estrogen therapy and depression in later life has been examined in some studies (Schiff *et al.*, 2005; Whooley *et al.*, 2000), very few have examined the effects that hormonal exposure across the lifetime may have on later life depression. In the fields of breast cancer and osteoporosis, it has been shown that lifetime exposure to estrogen is a better predictor of risk than individual exposure at any given moment (Clavel-Chapelon, 2002; Nguyen *et al.*, 1995). Therefore it appears that exposure to estrogen may be cumulative across a woman's reproductive life, and the effects long-lasting, continuing into late-life.

The objective of this study was to examine lifetime reproductive characteristics that are known to influence hormonal exposure and to determine whether these factors are associated with late-life depressive symptoms. We aim to develop a risk function of endogenous and exogenous hormonal factors, which could be used to identify individuals who are most at risk of developing depression late in life.

METHOD

Study population

The data used for this analysis were derived from a general population study of psychiatric disorders in the elderly French community (ESPRIT Study). Eligible participants, who were at least 65 years of age and non-institutionalised, were recruited from the electoral rolls in Montpellier between 1999 and 2001. After obtaining written informed consent from all participants, they were administered interviews by trained staff and underwent a number of clinical examinations at baseline and every two years thereafter. The ESPRIT study has been described in further detail elsewhere (Ritchie *et al.*, 2004).

Lifetime reproductive characteristics

From work undertaken most notably in the field of breast cancer, an increasing number of reproductive years, resulting from a younger age at menarche and/or an older age at menopause, would correspond to a higher lifetime endogenous estrogen exposure. On the other hand, estrogen exposure is expected to decrease with parity and an earlier age at child birth, and with fewer reproductive cycles before the first full-term pregnancy (resulting from a later age at menses and/or an earlier age at first childbirth). The type of menopause is also expected to influence estrogen exposure, as surgical menopause results in a more dramatic decline in estrogen levels than a natural menopause.

A specific questionnaire concerning reproductive lifetime events and hormonal exposure was administered as part of a general clinical examination. Information was recorded on the participant's age at menarche, number of children (full-term pregnancies, FTP), age at the birth of first and last child, age at menopause (defined as 1 year without menses) and type of menopause (i.e. natural, surgical or following a treatment such as chemotherapy). Information was also recorded on the participant's use of exogenous hormonal treatment, including oral contraceptives and HT, and the duration of such treatment.

For this analysis, two additional duration variables were generated; the "number of reproductive years", being the difference between the age at menopause and the age at first menses, and "number of reproductive years before the first FTP" (FFTP), calculated as the difference between age at the birth of the first child and age at first menses.

Depression measures

The Centre for Epidemiology Studies Depression Scale (CES-D) is a 20-point questionnaire designed to measure current depressive symptoms in the general population and has been validated in the elderly (Berkman *et al.*, 1986). As part of the baseline interview, participants were asked to respond to this questionnaire and were scored according to their responses, with a total score ranging from 0 to 60. It has been suggested that a cutoff point of 23 or more can be used to identify major depressive disorder (Radloff and Locke, 1986). A self-reported history of past depressive episodes was included as a covariate in this analysis.

Other measures

Potential confounding factors were selected based on the literature and included: age, educational level, marital status, insomnia, physical disability, cognitive impairment and comorbidity. In addition we considered the effect of antidepressants and other types of medication currently used (excluding hormonal treatment). All types of medications were validated by presentation of the prescription or the medication itself. Participants were classified as disabled if they were unable to complete at least one task from either the Instrumental Activities of Daily Living (IADL) (Lawton and Brody, 1969) or the Activities of Daily Living (ADL) (Katz *et al.*, 1963) scales. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975). Participants scoring less than the 10^{th} percentile for their age (4 groups) and education level (4 groups), were classified as cognitively impaired. This method of classifying cognitive impairment, compared with that based on an unadjusted MMSE score <26, did not change the results of the study. 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 (Ribet and Derriennic, 1999). Comorbidity was defined as having a history of vascular diseases (including angina pectoris, myocardial infarction, stroke, cardiovascular surgery, bradycardia or palpitations) or a cancer diagnosis within the last 2 years.

Statistical Analysis

Two-tailed chi-squared tests or t-tests were used to compare categorical and continuous characteristics respectively, between depressed and non-depressed women. Logistic regression models, adjusting for only age and education level were initially generated to identify the hormonal factors which appeared to have some association with current depressive symptoms. All factors with a significance level of $p<0.2$ in these models were retained for the multivariate models. For the variables which were treated as continuous the linearity assumption for logistic regression was assessed by firstly categorising the variable into multiple equal groups and plotting each group's coefficient against the midpoint of that group. The method of fractional polynomials also confirmed inclusion of a continuous variable in the model.

In the multivariate models we adjusted for age (continuous), education level (≥12 years of education), marital status (married or a couple vs. widowed, divorced, separated or single), disability, cognitive impairment, insomnia and current use of medication (>3 different medications), to determine if any of the hormonal variables were independent predictors of depressive symptoms. Additional analyses examined the effect of adjusting for antidepressant treatment and a self-reported history of past depression. All of the final models passed both the Hosmer-Lemeshow and the Pearson goodness-of-fit tests. SAS version 9.1 (SAS Institute, Inc., North Carolina) was used for the statistical analysis with a significance level of $p<0.05$.

RESULTS

The 1013 participants described in this analysis were those who had completed the hormonal questionnaire and for whom full data was available on depression status and all other covariates included in the multivariate models. Women with diagnosed dementia were excluded from this analysis. The 300 women not included in the present study were older (t= -4.88, df=1311, $p<0.001$) and had a lower educational level (χ^2 =16.9, df=1, $p<0.001$). They were more likely to have disabilities (χ^2 =58.4, df=1, $p<0.001$), cognitive dysfunction (χ^2 =36.4, df=1, $p<0.001$), comorbidity (χ^2 =4.9, df=1, p=0.027) and take more than 3 medications (χ^2 =8.7, df=1, p=0.003). The excluded participants were also more likely to be depressed (χ^2 =6.4, df=1, p=0.012), have past depression (χ^2 =17.8, df=1, $p<0.001$) and use antidepressants (χ^2 =11.2, df=1, $p<0.001$), but were significantly less likely to use or have used HT (χ^2 =6.9, df=2, p=0.03), than the participants described here. There was no significant difference in terms of the other hormonal factors between the excluded subjects and those included in this analysis.

Population characteristics

The characteristics of the 1013 women in this study are given in Table 1, according to their depression status. The women had a mean age of 72.9, ranging from 65 to 94 years. The majority of women had less than 12 years of education, and approximately half were married or in a stable relationship. The prevalence of depressive symptoms (CES-D≥23) was 16.9% and women with depression differed significantly from those without depression with regard to all of the characteristics examined. Depressed women were older, less educated and were less likely to be married or have a partner. The percentage of depressed women who had physical disabilities was almost three times that of non-depressed women, and they were also more likely to have cognitive impairments, suffer from insomnia and use more than 3 medications. However, there was no difference between the percentage of women with comorbidity in the depressed and no-depressed groups and therefore this covariate was not considered further in the analysis. Among the participants, 13% reported a past depressive episode that corresponded to a period of hormonal variation (i.e. puberty, premenstrual period, pregnancy, or menopause), 26% reported non-hormone-related past depression only, and 21% both types of depression (data not shown). Women with current depressive symptoms were more likely to take antidepressants.

Prevalence and correlates of depression

The different reproductive characteristics that were examined in this study are given in Table 2. The mean age at reported first menses was 13.1 (range 9-21) and the mean age at menopause was 49.5 (range 28-63). Women had an average of 36.4 reproductive years, ranging from 12 to 53 years. Over 80% of the women in this study had a natural menopause. The majority of women had one, two or three children, with less than 10% nulliparous. Women in this sample tended to have their first child in their 20s, with an average of 11.9 (range 2-29) years before FFTP, and the age at the birth of the last

child was quite variable. Although this was an elderly cohort, oral contraceptive use during the reproductive years was not infrequent (18.7%), and a number of women were either past (19.8%) or current users (14.8%) of HT. Of the women who did use HT, they were more likely to have used it for at least 10 years.

Comparing the reproductive characteristics of the women with depressive symptoms to those without, we found no differences in the age at first menses, in the number of children or age at the birth of their first child, in the duration of HT or in the percentage of women who had natural menopause. On the other hand, the age at menopause and the number of reproductive years were significantly lower for depressed women, than for those without depression. Depressed women were also more likely to have had their last child either early or late in life, compared to the majority of women. With regard to exogenous hormone exposure, contraceptive use was higher among the non-depressed women, as was current use of HT, however past HT use was more common among those with depressive symptoms.

Crude associations between hormonal factors and depression

We examined firstly the individual associations between lifetime hormonal factors and depressive symptoms, while adjusting for the key covariates age and educational level (Table 3). Age at menopause rather than age at first menses was associated with depression, with the risk of depression decreasing by 4% (OR: 0.96) for each one-year increase in menopause age. The number of reproductive years, which is calculated as the difference between the age at menopause and the age at first menses, was also associated with depressive symptoms (OR: 0.97), however it was not a better predictor of depression than age at menopause alone. When women were compared according to type of menopause, we found no difference in risk for women who had a natural versus a surgical ($p=0.9$) or "other" type of menopause ($p=0.7$).

The odds of depression for women with up to 3 children and for women with 4 or more children, was not significantly different from that of nulliparous women. Likewise, there was no significant difference in the odds of depression between women who had their first child in their 20's or 30's, and those who had their first child before their 21st birthday. However, an earlier age at the birth of the last child was significantly associated with depression. In particular, women who had their last child between 26 and 34 years of age had a lower risk of depression than those who had their last child at a younger age (OR:0.51, 95%CI: 0.30-0.86).

With regard to exogenous hormonal treatment, long-term oral contraceptive use (≥10 years), compared to never use, appeared to have a beneficial effect on the risk of depression (OR: 0.38, 95% CI: 0.13-1.07). Past but not current use of HT was associated with a significantly increased risk of depression compared to never use (OR: 1.62, 95% CI: 1.08-2.42), while there was no increased risk for either a short or longer duration of treatment. This raw analysis was used as a means of screening for the hormonal factors which appeared to be associated with depression, and any factor with $p<0.2$ was retained for further analysis.

Multivariate adjusted associations between hormonal factors and depression

Age at menopause (rather than reproductive years), age at birth of the last child, duration of OC use and HT use, were considered together in an initial model, adjusting for age and educational level. With the simultaneous addition of these hormonal factors in the model, age at birth of the last child no longer remained significant. On the other hand, both an early age at menopause and past HT use remained associated with depression (Model 1, Table 4) and a longer duration of OC use significantly decreased the odds of depressive symptoms.

Interaction terms between the hormonal factors in model 1 and the covariates age and education were then examined and educational level was shown to modify the effect of age at menopause on depression. For women with lower education (<12 years of schooling), age at menopause was significantly associated with the odds of depression, however for women in the higher education group the association was not significant (Model 2).

We then determined whether the hormonal factors remained significantly associated with depression after controlling for a number of important covariates in addition to age and educational level. Model 3 shows that, after further adjusting for marital status, insomnia, the number of medications currently used, physical disabilities and cognitive impairment, the three hormonal variables remained significant. For women with lower education only, an increasing age at menopause was significantly associated with a decreased risk of late-life depression (linear effect, OR: 0.95, 95%CI: 0.91-0.99). For all women, long-term oral contraceptive use compared to never use, was shown to be beneficial in reducing the risk of late-life depression (OR: 0.33, 95% CI: 0.11-0.96). In contrast, past HT appeared to be a risk factor for depressive symptoms (OR: 1.63, 95% 1.07-2.50).

Finally we generated a model controlling for current antidepressant use and a past history of depression, in addition to the other covariates (Model 4). These factors were added in a separate model, as we realised their addition could result in over-controlling. However, as shown, adjustment for these factors had a minimal effect on the associations found.

Using model 4, we also examined the effect of controlling for the type of menopause, despite its non-significant association with depressive symptoms, and additionally generated a model using only the subjects who had had a natural menopause (data not shown). The odds ratios for the hormonal factors remained very similar, however the significance levels did drop, most likely due to the smaller sample size (exclusion of an additional 186 women with a non-natural menopause).

DISCUSSION

The aim of this study was to determine key hormonal determinants of late-life depressive symptoms. Depression is a common end-point of multiple aetiological pathways, implicating a large number of causal factors whose individual influence may be quite small. Despite this, we were able to show a clear link to hormonal factors in elderly women. These risk factors remained significant even after adjusting for a large number of covariates. Our results indicate a strong inverse relationship between menopausal age and late-life depression, but only for women with a lower education. On the other hand, in all women, exogenous hormonal treatment appeared to influence depressive symptoms.

Endogenous hormonal exposure

The number of reproductive years, calculated as the difference between age at menopause and age at menarche, is often used as an indirect measure of lifetime estrogen exposure (Low *et al.*, 2005). In this study, we found that an increasing number of reproductive years were associated with an increased risk of depressive symptoms. However this was not a better measure of depression risk than age at menopause alone and in fact, there was no significant association between menarche age and depression. Among the participants in this study, there was less variation in the age at menarche, with over 75% of the women reporting that their first menses was between 11 to 14 years of age, which may explain the lack of association with depression. On the other hand, the reported age at menopause was much more variable, even if we considered only the women with a natural menopause. Higher inaccuracy in the recorded information regarding early lifetime events appears unlikely, other studies having reported that up to 90% of women could correctly report menses within a 1 year error margin (Bean *et al.*, 1979).

Of the few studies which have examined the influence of reproductive characteristics on the development of depressive symptoms later in life, an earlier onset of menopause has been cited previously as a risk factor (Harlow *et al.*, 2003). In addition, our results further suggest that the effect of menopausal age is not equal across all subjects, with only women in the lower education group being at risk of depression from a lower age at menopause.

We found no other positive associations between late-life depressive symptoms and the other reproductive factors which are known to effect endogenous exposure such as nulliparity (McLay *et al.*, 2003) and later age at the birth of children (Kalache *et al.*, 1993), the latter appearing significant only when examining associations adjusted for age and education but not in multi-adjusted models. These results therefore do not support the hypothesis that lifetime endogenous estrogen exposure is a predictor of late-life depression. However, the negative association between menopause age and risk of late-life depression suggests that the number of years post-menopausal could be a key to predicting the risk of depression. It could be that the amount of time spent in an estrogen-deprived state is a more crucial factor for elderly women than cumulative exposure to estrogen across the lifetime.

Exogenous hormonal exposure

Both oral contraceptives and HT could increase exogenous steroid exposure, however our study suggests that these treatments have differing effects on late-life depressive symptoms. Long-term oral contraceptive use (≥10 years) significantly decreased the odds of a woman having depressive symptoms, while past HT use, but not current use, was a significant risk factor for depression, when compared to women who never used treatment.

It has previously been suggested that the effects of the contraceptive pill on other hormone-dependent disorders in later life, are more pronounced when the pill is taken closer to the menopause (Key *et al.*, 2001; Michaelsson *et al.*, 1999). Our study supports these observations. In France, legislation concerning the oral contraceptive pill came into effect in 1967, and therefore, given the age of our study population, women who were long-term users of oral contraceptives, were also likely to be those who used treatment in their late reproductive life. Thus, our results indicate also that oral contraceptive use later in life may be more beneficial.

Our findings concerning HT use are more surprising, and contribute to the uncertainty surrounding its use. It has been reported that HT can have beneficial effects on depressed mood (Whooley *et al.*, 2000), however our results support the majority of studies indicating no association between current use and depression in post-menopausal women (Cohen *et al.*, 2003). On the other hand, this study is one of very few to report the past HT may have a negative impact on late-life depressive symptoms. This raises the question of when women stopped their treatment and their reasons for stopping. Women who are on treatment but develop worse depressive symptoms may discontinue use, or could change to antidepressants instead. Women with increased cardiovascular risk are also more likely to discontinue HT, and cardiovascular factors have bee associated with depression. In addition, women with depressive symptoms may also be more likely to complain of menopausal symptoms and thus to be prescribed HT (bias of indication). Indeed, we observed that past or current HT users had a more frequent history of past depression than never users (data not shown). In spite of this, only past HT users had a higher risk of late-life depression, suggesting perhaps a more beneficial effect of current HT use on depressive symptoms.

In general, women undergoing menopause at an earlier age, or those with a surgical menopause, are more likely to be HT users and HT use among these women may have more beneficial effects (Kotz *et al.*, 2006). However, in this study the positive association between depression and past HT use remained significant with the inclusion of menopausal age in the model and even after controlling for the type of menopause (natural, surgical or other). In addition, an interaction term between HT and age at menopause was not significant in the final model. Other explanations for the negative effect of past but not current HT, could relate to the different treatments which were administered in France in the last decades. Past users were more likely to be prescribed oral estrogen or combined oral estrogen-progestogen preparations, while current HT use is more likely to be transdermal. It is also possible that there were more inaccuracies in the reporting of past HT use, as

fewer women were able to recall the type of treatment that was given. For current HT users, on the other hand, the medication type was verified via the prescription or the box of medication itself.

Overall these results do not support a beneficial effect from cumulative endogenous estrogen exposure in postmenopausal women, but indicate that hormonal events later in life, such as menopausal age, long-term oral contraceptive use and HT, may play a greater role in predicting depressive symptoms.

Limitations

A limitation of the present study is that the data collected from the hormonal questionnaire were both self-reported and retrospectively assessed. This could lead to inaccuracies in the recorded information particularly because it concerns elderly people and events during the reproductive lifetime, some of which occurred many decades before. However, it has been reported that women recall reproductive events with a high degree of accuracy (Bean *et al.*, 1979). In addition, there is no clear reason why depressed women would have recalled their exposures less precisely than non-depressed women (participants were not unaware of the hypothesis being tested in this analysis), and therefore any errors should not have biased the results found.

There is also the potential for bias in this analysis, due to the exclusion of women from the ESPRIT population who had missing data for at least one of the variables analysed here. These women who had overall poorer health, were more likely to be depressed, thus decreasing the overall power of the study. In terms of the hormonal variables however, there was very little difference between the excluded women and those analysed here, and therefore this probably had only a minimal effect on our findings.

The study size was not large enough to examine the different types of oral contraceptive treatments and HTs, which may have had varying effects on late-life depressive symptoms, in particular estrogen versus combined estrogen-progesterone preparations. In addition, there is a bias of prescription in regards to women who are given HT and therefore, despite controlling for a number of variables related to this, other factors which were not considered, may have influenced the results. In addition, while significant associations were found, no conclusions can be drawn from this cross-sectional analysis about the causal relationship.

Strengths

Despite these limitations, this study has a number of strengths. The data used in this analysis come from a large population-based study and therefore the results are relevant to elderly women living in the community, cover a wide variety of exogenous exposure patterns and due to large numbers, was able to take into account numerous covariates linked to depressive symptoms and their interactive effects. We have used a measure of depressive symptoms which has been validated in the elderly (Berkman *et al.*, 1986) and appears to be a indicator of major depressive disorder (Radloff and Locke, 1986).

At 4-years follow-up of the ESPRIT study, 12% of the women responded to a number of questions that had already been asked at the baseline interview, including their age at menopause. The overall concordance in responses was very good, suggesting the high quality of data that has been used for this analysis. In addition, because detailed information was obtained on all of the participants in this study, we were able to adjust for a range of factors in the multivariate analysis, thus minimising any confounding.

To our knowledge, this is the first study to examine the association between a number of lifetime reproductive/hormonal factors and late-life depressive symptoms. Our work suggests that menopausal age could be used as a marker to identify women who have an increased risk of developing depression late in life. In particular, for women with a low level of education, an early age at menopause appears to be a strong risk factor. Exogenous OC and HT use were shown to modify the risk of late-life depression. Further work is needed to clarify the mechanisms underlying these associations, and in particular the effects of the type of HT used. While much previous research has focused on whether all women should or should not use HT, our research suggests that if such treatment is truly beneficial, and the risk of secondary adverse effects is low, it is probably best suited to a subgroup of "hormone-sensitive" women, who may be more susceptible to the effects of estrogen exposure across their lifetime. Obviously recognised contraindications of HT use have to be taken into account (Anderson *et al.*, 2004). Natural formulations are preferable given their probably lower side effects and their potentially greater impact on neuropsychiatric disorders (Ancelin *et al.*, 2007). In this case HT prescription should be preceded by a screening examination to determine probability of real benefit, rather than generalized prescription to all women.

Conflict of interest declaration

The ESPRIT project is financed by the regional government of Languedoc-Roussillon, a grant from the Agence Nationale de la Recherche (ANR) and an unconditional grant from Novartis. Joanne Ryan is the recipient of a France Alzheimer grant.

None of these sponsors had any involvement or say in the study design, data collection, data analysis or in the decision to publish.

Description of authors' roles: J. Ryan generated the working hypotheses for this study in collaboration with M-L Ancelin, performed the statistical analysis and wrote the manuscript. I. Carrière supervised analysis and assisted with manuscript revision. K. Ritchie is chief investigator of the ESPRIT study and assisted with manuscript revision. J. Scali was responsible for the data management. M-L. Ancelin designed the study, and had a major role in reviewing the paper.

TABLE 1. Characteristics of participants with or without high depressive symptoms.

Characteristic	CESD <23 n = 842	CESD ≥23 n = 171		
	Mean (sd)		t-value (df)	p-value
Age	72.8 (5.5)	73.8 (5.5)	-2.3 (1011)	0.02
	Percentage		χ^2 Statistic (df)	p-value
≥12 years of education	44.2	35.7	4.20 (1)	0.040
Single, divorced, separated or widowed	45.0	55.0	5.66 (1)	0.017
Disability[a]	3.6	9.9	13.07 (1)	<0.001
Cognitive impairment[b]	15.7	31.2	12.13 (1)	< 0.001
Currently using medication[c]	44.3	60.8	15.57 (1)	< 0.001
Insomnia	20.2	45.0	47.56 (1)	<0.001
Comorbidity[d]	16.8	17.1	0.008 (1)	0.93
Antidepressant use	5.0	17.5	32.94 (1)	< 0.001
Past Depression	37.3	57.9	24.98 (1)	< 0.001

[a] According to Instrumental Activities of Daily Living (IADL) and the Activities of Daily Living (ADL) criteria.

[b] A Mini Mental State Examination score (MMSE) of less than the 10th percentile, after adjusting for age and education.

[c] Includes all medication currently being prescribed other than hormonal treatment or antidepressants (>3 medications).

[d] Includes cardiovascular disease, other heart problems or cancer diagnosed within the last 2 years.

TABLE 2. Lifetime reproductive characteristics, according to depression status.

Reproductive Characteristic	CESD <23 *n = 842*	CESD ≥23 *n = 171*		
	Mean (sd)		**t-value (df)**	**p-value**
Age at 1st Menses	13.1 (1.6)	12.9 (1.6)	1.12 (1011)	0.26
Age at Menopause	49.7 (5.1)	48.5 (5.6)	2.66 (1011)	0.008
Number of Reproductive Years [a]	36.6 (5.3)	35.5 (5.8)	2.22 (1011)	0.012
Number of Years before FFTP[b*]	***n = 740***	***n = 149***		
	11.9 (4.2)	11.8 (4.1)	0.26 (1011)	0.80
	Percentage		**χ^2 Statistic (df)**	**p-value**
Type of Menopause			0.29 (2)	0.87
Natural	81.3	82.1		
Surgical	9.7	10.1		
Other (i.e. treatment-related)	9.0	7.8		
Number of Children			0.57 (2)	0.75
0	9.8	9.3		
1, 2 or 3	69.3	72.2		
>3	20.9	18.5		
*Age at birth of 1st child**	***n = 740***	***n = 149***	1.01 (2)	0.61
≤ 20	10.7	13.4		
21 - 29	75.4	73.8		
≥ 30	13.9	12.8		
*Age at birth of last child**	***n = 678***	***n = 138***	7.51 (2)	0.023
≤ 25	11.5	18.4		
26 - 34	61.4	50.0		
≥ 35	27.1	31.6		
Oral Contraceptive Use			6.35 (2)	0.042
Never	81.0	83.0		
0 – 9 years	11.8	14.6		
≥ 10 years	7.2	2.3		
Hormonal Treatment (HT)			4.84 (2)	0.089
Never	66.0	62.0		
Past	18.7	25.7		
Current	15.3	12.3		
Duration of HT			0.67 (2)	0.72
Never	66.0	62.0		
0 – 9 years	15.1	17.5		
≥ 10 years	18.4	18.7		

[a] Calculated as the difference between the age at menopause and the age at first menses.

[b] First Full-Term Pregnancy (FFTP): the difference between the age at the birth of the first child and the age at first menses.
* This analysis involved a smaller number of women due to additional missing values because some women did not have any children (n=97), others did not report the age at the birth of their first child (n=27), the age at the birth of their last child, while others had only 1 child (n=102).

TABLE 3.

Crude associations between lifetime reproductive factors and depressive symptoms.

Reproductive Characteristic	Group	Odds ratio [95% CI]	χ^2 statistic (df)	p-value*
Age at first Menses		0.95 [0.85 - 1.05]	0.99 (1)	0.32
Age at Menopause		0.96 [0.93 - 0.99]	6.03 (1)	0.014
Number of Reproductive Years		0.97 [0.94 - 1.00]	4.31 (1)	0.038
Number of Years before 1st FFTP		1.00 [0.95 - 1.04]	0.05 (1)	0.83
Type of Menopause	Natural	1		
	Surgical	1.02 [0.59 - 1.78]	0.005 (1)	0.94
	Other	0.89 [0.48 – 1.66]	0.13 (1)	0.72
Number of Children	0	1.0		
	1, 2, 3	1.12 [0.62 - 2.02]	0.14 (1)	0.71
	≥ 4	0.96 [0.49 - 1.88]	0.02 (1)	0.90
Age at birth of 1st Child	≤ 20	1.0		
	21 - 29	0.76 [0.45 - 1.31]	0.97 (1)	0.33
	≥ 30	0.73 [0.36 - 1.47]	0.78 (1)	0.38
Age at birth of last Child	≤ 25	1.0		
	26 - 34	0.51 [0.30 - 0.86]	6.33 (1)	0.012
	≥ 35	0.69 [0.39 - 1.22]	1.59 (1)	0.21
Oral Contraceptive use	Never	1.0		
	0 – 9 yrs	1.47 [0.89 - 2.41]	2.27 (1)	0.13
	≥ 10 yrs	0.38 [0.13 - 1.07]	3.39 (1)	0.066
Hormonal Treatment (HT)	Never	1.0		
	Past	1.62 [1.08 - 2.42]	5.50 (1)	0.019
	Current	1.09 [0.64 - 1.86]	0.10 (1)	0.75
Duration of HT use	Never	1		
	0 – 9 yrs	1.35 [0.85 - 2.15]	1.32 (1)	0.21
	≥ 10 yrs	1.31 [0.83 - 2.08]	1.58 (1)	0.25

* Adjusted for age and education

TABLE 4.

Multivariate adjusted models for the association between lifetime reproductive characteristics and depressive symptoms.

	MODEL 1[a]		*MODEL 2*[a]		*MODEL 3*[b]		*MODEL 4*[c]	
	OR [95% CI]	**χ^2 stat.[d], (p-value)**	**OR [95% CI]**	**χ^2 stat.[d], (p-value)**	**OR [95% CI]**	**χ^2 stat.[d], (p-value)**	**OR [95% CI]**	**χ^2 stat.[d], (p-value)**
Age at Menopause for:	0.97 [0.94 - 0.99]	5.16 (0.02)						
< 12yrs educ.			0.94 [0.91 - 0.98]	10.1 (0.002)	0.95 [0.91 - 0.99]	7.16 (0.007)	0.95 [0.91 - 0.99]	6.34 (0.012)
≥12yrs educ.			1.01 [0.91 - 1.12]	0.05 (0.82)	1.03 [0.92 - 1.14]	0.21 (0.66)	1.02 [0.91 - 1.13]	0.09 (0.76)
Oral Contraceptives								
Never	1.0		1.0		1.0		1.0	
0 – 9 yrs	1.53 [0.92 - 2.54]	2.70 (0.10)	1.50 [0.91 - 2.49]	2.47 (0.12)	1.49 [0.87 - 2.54]	2.13 (0.15)	1.39 [0.80 - 2.39]	1.37 (0.24)
≥ 10 yrs	0.41 [0.15 – 1.18]	2.73 (0.09)	0.40 [0.14 – 1.14]	2.97 (0.09)	0.33 [0.11 – 0.96]	4.18 (0.04)	0.32 [0.11 - 0.93]	4.37 (0.04)
Hormone Therapy								
Never	1.0		1.0		1.0		1.0	
Past	1.62 [1.08 - 2.43]	5.43 (0.02)	1.60 [1.07 - 2.41]	5.13 (0.02)	1.63 [1.07 - 2.50]	4.98 (0.03)	1.56 [1.00 - 2.34]	3.87 (0.05)
Current	1.09 [0.64 - 1.88]	0.10 (0.75)	1.11 [0.65 - 1.91]	0.14 (0.71)	1.13 [0.64 - 1.98]	0.18 (0.67)	1.10 [0.62 - 1.94]	0.10 (0.76)

[a] Adjusted for age and educational level only

[b] Adjusted for age, educational level, marital status, insomnia, disability, cognitive impairment, number of drugs.

[c] Adjusted for age, educational level, marital status, insomnia, disability, cognitive impairment, number of drugs, as well as past depression and antidepressant treatment.

[d] Test-statistic was compared to a χ^2 distribution with 1 degree of freedom.

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