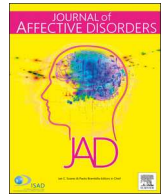




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Short communication

Severe insomnia is associated with metabolic syndrome in women over 50 years with major depression treated in psychiatry settings: a METADAP report

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ABSTRACT

Introduction: Major depression is associated with metabolic syndrome and cardiovascular risk. We have previously shown that severe insomnia, a core symptom of major depression episode (MDE), is associated with hypertriglyceridemia, a component of metabolic syndrome, in women but not in men with major depression. Since insomnia is related to cardiovascular morbidity in the general population and major depression also, our objective was to assess the link between insomnia and metabolic syndrome, a marker syndrome of cardiovascular risk, during MDE, in women and in men.

Methods: In 624 patients with a current MDE cohort, both insomnia and metabolic syndrome were assessed in women and men. Insomnia was rated from 0 to 6 based on the HDRS corresponding items, severe insomnia being defined by a total insomnia score ≥ 4 .

Results: severe insomnia was associated with metabolic syndrome in women but not in men. In multivariate logistic regressions, these results in women were independent from age, educational level, major depressive disorder duration and current smoking. These results were only significant in women aged ≥ 50 years, a cut-off age for menopausal status but not in women under 50 years.

Conclusion: Women aged ≥ 50 years with a severe insomnia during MDE have an increased risk of metabolic syndrome. Severe insomnia may be a clinical marker of metabolic risk in this population. They should be particularly monitored for metabolic syndrome and may benefit from sleep recommendations and cardiovascular prevention.

Abbreviations: BP, Blood pressure; HDL, High Density Lipoprotein; HDRS, Hamilton Depressive Rating Scale; IDF, International Diabetes Federation; MetS, Metabolic Syndrome; MDD, Major Depressive Disorder; MDE, Major Depressive Episode; NCEP ATP III, National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

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1. Introduction

Major depressive disorders (MDD) and cardiovascular diseases are two main public health issues, which are the first and second leading causes of disability worldwide respectively (WHO | Cardiovascular diseases (CVDs) [Internet]. WHO 2019; WHO W. WHO | Depression and Other Common Mental Disorders [Internet]. WHO Depression 2017)).

Metabolic syndrome (MetS) is a clinical and biological combination of metabolic criteria aimed at identifying and preventing cardiovascular risk (Huang, 2009), ie cardiovascular events and death (Gami et al., 2007; Galassi et al., 2006; Mottillo et al., 2010). Currently, the most used criteria for MetS are those from the National Cholesterol Education Program, NCEP ATP III (National Cholesterol Education Program (NCEP) 2002) and the International Diabetes Federation, IDF Alberti et al., (2005).

Numerous studies linked MetS and MDD (De Hert et al., 2018). Indeed, based on a meta-analysis involving 5531 patients, Vancampfort et al. showed that the MetS prevalence is around 30% in MDD, which is 1.5 times higher compared to the general population (Vancampfort et al., 2014). The association of MetS and MDD results in a two- to three-fold higher cardio-vascular mortality in patients with MDD (Correll et al., 2017; Lichtman et al., 2017).

Because MDD is a heterogeneous disorder, some studies looked at subtypes of major depression linked with cardiovascular risk (Case et al., 2018; Roest et al., 2011; Smolderen et al., 2009). However, results are inconsistent and need more studies to define endophenotypes with a strong association with cardiovascular risk (Lichtman et al., 2014).

Insomnia, a core symptom of MDE (Franzen and Buysse, 2008), has been linked to cardiovascular risk and diseases, with data about elevated blood pressure, coronary heart disease and heart failure (Javaheri and Redline, 2017). Furthermore, previous studies showed that insomnia is linked with an increased risk of mortality during cardiovascular disease (Javaheri and Redline, 2017; Sofi et al., 2014; Li et al., 2014; Parthasarathy et al., 2015), these findings being consistent across studies. However, these results have not yet been assessed in MDD subpopulations.

Using METADAP cohort data, we previously described that hypertriglyceridemia (triglyceridemia ≥ 200 mg/dL) is linked to severe insomnia during MDE, especially in women but not in men. Women with severe insomnia exhibit a 4.5-fold higher prevalence of hypertriglyceridemia than women without severe insomnia (Costemale-Lacoste et al., 2017).

Since hypertriglyceridemia is a component of MetS, we investigated the association of severe insomnia with MetS in women and men in a large population of patients with a current diagnosis of MDE in a context of MDD. Our objectives were to investigate whether insomnia, especially severe insomnia, is associated with 2 main definitions of MetS which are NCEP ATP III and IDF in patients suffering from a current MDE. Because metabolism and prevalence of MetS in men and women show a wide disparity we assessed our hypotheses by sex.

2. Methods

2.1. Design and participants

Data were drawn from the baseline of the METADAP study (Corruble et al., 2015), a cohort of individuals aged 18–65 years with a diagnosis of current MDE in a context of MDD, with a Hamilton Depression Rating Scale (HDRS) ≥ 18 (Hamilton, 1960). This multisite naturalistic study included patients from 6 French university psychiatric departments.

The diagnosis was ascertained by the MINI International Neuropsychiatric Interview. Psychotic features during the MDE, a diagnosis of psychotic disorders, bipolar disorders, eating disorders or

current substance abuse or dependence (including alcohol use disorder but excepted tobacco use) (DSMIV-TR), psychostimulant or anti-psychotic drugs use, pregnancy, organic brain syndromes or severe unstable medical conditions were non-inclusion criteria.

Clinical assessments were performed by trained psychiatrists and psychologists.

Each participant provided written informed consent. The study was registered by the French National Agency for Medicine and Health Products Safety and the Commission Nationale de l'Informatique et des Libertés, was approved by the Ethics Committee of Paris-Boulogne, France, and conformed to international ethical standards (ClinicalTrials.gov identifier: NCT00526383). The study was conducted in accordance with the Helsinki Declaration.

2.2. Measures

2.2.1. Insomnia

Insomnia was assessed based on the 3 items of the HDRS-17: difficulty falling asleep, difficulty staying asleep, and early morning awakenings. Each item was rated from 0 to 2 depending on the symptom presence and severity. The total insomnia score was the sum of the 3 item scores (0–6) (Manber et al., 2005). As described by our previous works, severe insomnia was defined based on a total insomnia score ≥ 4 , corresponding to a maximum rating on 2 out of 3 insomnia items (Costemale-Lacoste et al., 2017; Costemale-Lacoste et al., 2018). Severe insomnia (yes/no) was the main explicative variable.

2.2.2. Metabolic syndrome

Two definitions of MetS were used. The first one has been published by the National Cholesterol Education Program (NCEP ATP III) (National Cholesterol Education Program (NCEP) 2002) and the second by the International Diabetes Federation (IDF) (Alberti et al., 2005). According to the NCEP ATP III criteria, the presence of any three of the following five components is required for a diagnosis of MetS: abdominal obesity, hypertriglyceridemia (triglyceridemia ≥ 1.7 mmol/L); low HDL cholesterolemia (HDL cholesterolemia ≤ 1.03 mmol/L for men and ≤ 1.29 mmol/L for women); elevated blood pressure (BP) (systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg or current use of antihypertensive drugs); impaired fasting glycemia (fasting plasma glycemia ≥ 5.6 mmol/L). The IDF MetS diagnosis requires the presence of waist circumference ≥ 94 cm for men and ≥ 80 cm for women plus any two of the followings: fasting plasma glycemia ≥ 5.6 mmol/l (or type 2 diabetes mellitus), serum triglycerides ≥ 1.7 mmol/l, serum HDL cholesterol < 1.03 mmol/l for men (or < 1.29 mmol/l for women) and/or BP $\geq 130/85$ mmHg.

Of note, past history of coronary heart disease has not been assessed.

2.3. Statistical analyses

Bivariate analyses were performed, comparing whole sample, men and women using independent samples t-tests and the Pearson Chi-squared tests as appropriate. To assess the association between insomnia and MetS (yes/no), t-tests (total insomnia) or Chi-squared tests (severe insomnia) were used. Logistic regressions (severe insomnia: yes/no) were used to investigate whether MetS according to the NCEP ATP III and IDF definitions remained associated with severe insomnia, independently from covariates. Covariates were chosen "a priori" for their usual effect on MetS and for their association with MetS in bivariate analyses: age (Dominguez and Barbaggio, 2016), current tobacco smoking (Yankey et al., 2016), educational level (Kim et al., 2017; Moore et al., 2017; Montano, 2017), diabetes status and MDD duration (Hiles et al., 2016) or number of previous MDE (Ajatunmobi et al., 2013) were included as covariates. MDD duration

and number of previous MDE were not included in the same model because of their collinearity. In order to support sex specific analyses, we conduct a supplemental multivariate logistic regression model including the interaction variable sex*insomnia. Moreover, because menopausal status is linked with obstructive sleep apnea (Eichling and Sahni, 2005) and MetS (Marchi et al., 2017; Gurka et al., 2016), we conducted a supplementary analysis in which we selected women aged ≥50 years, because this age is considered as a cut-off value for menopausal transition (Sherman, 2005). Results were expressed in odd-ratio (OR) and their 95% confidence interval (95%CI). Statistical significance was evaluated using two-sided tests with an alpha risk set a priori at 0.05. Statistical analyses were performed using SPSS 20 software (IBM SPSS Statistic 20).

3. Results

3.1. Sociodemographic characteristics

624 patients, consisting of 433 (69.4%) women and 191 (30.6%) men were analyzed in METADAP study (Corruble et al., 2015). The 2 groups did not differ in terms of age, educational level, HDRS severity, MDD duration, antidepressant previous duration, diabetes status and current smoking. We did not find any between group difference in insomnia, severe insomnia and prevalence of MetS. Table 1 summarize the main characteristics of the population.

3.2. Association of insomnia and MetS in the whole sample

Bivariate analyses did not find any difference between patients with or without severe insomnia (Table 2). The prevalence of MetS was 25% vs 19%, ($p = 0.1$) (NCEP ATP III) and 32% vs 24%, ($p = 0.3$). Controlling for age, sex, current smoking, education level, diabetes status and duration of the MDD in multivariate logistic regression confirm these results (Table 2): severe insomnia was not associated with MetS (NCEP ATP III or IDF definitions) in the whole sample.

We found an interaction between sex and severe insomnia OR = 3.6 [1.5–8.7] ($p = 0.004$) (NCEP ATP III) and 3.2 [1.4–7.3], ($p = 0.006$) (IDF). This prompted us to perform sex-specific analyses (Table 2).

Table 1

Comparison of men and women for socio-demographic variables, insomnia and MetS prevalence.

	Women (n = 433)	Men (n = 191)	p
Age m(sd)	45.8 (13.6)	46.9 (12.1)	0.3
Educational level n(%)			
Low	37 (8.5)	19 (9.9)	0.4
Middle	206 (47.6)	83 (43.5)	
High	190 (43.9)	89 (46.6)	
Total HDRS m(sd)	24.7 (4.9)	24.7 (5.0)	0.9
Suicide attempt history n(%)	108(25.1)	37 (19.6)	0.1
MDD duration m(sd)	10.9 (11.4)	8.5 (12.1)	0.2
Antidepressant previous duration (years) m(sd)	2.4 (4.1)	2.1 (4.3)	0.3
Current smoking n(%)	155 (36)	75 (39)	0.4
Total insomnia m(sd)	3.5 (1.8)	3.5 (1.9)	0.9
Severe Insomnia n(%)	234 (54)	101 (53)	0.8
Diabetes n(%)	28 (6.4)	14 (7.3)	0.7
MetS NCEP n(%)	88 (2)	51 (27)	0.08
MetS IDF n(%)	115 (27)	59 (31)	0.3

Abbreviations: m(sd): mean standard deviation; HDRS: Hamilton Depressive Rating Scale; MetS NCEP: Metabolic syndrome definition from National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III); MetS IDF: Metabolic Syndrome from the International Diabetes Federation. Education Levels: Low(primary school), Middle(high school), High(post graduate).

3.3. Association of insomnia and MetS in women

In women, bivariate analyses showed a positive significant association between insomnia (total or severe) and MetS for the two international definitions. The prevalence of MetS in women with severe insomnia versus those without severe insomnia was, 25% vs 14% ($p = 0.006$) (NCEP ATP III), and 31% vs 22% (IDF) ($p = 0.03$) (Table 2).

Controlling for age, current smoking, education level, diabetes status and duration of the MDD in multivariate logistic regressions confirm our findings. Severe insomnia remained positively associated with MetS, with an OR = 2.2, 95%CI [1.3–3.9], ($p = 0.004$) for NCEP ATP III, and OR = 1.8, 95% CI [1.1–2.9], ($p = 0.02$) for IDF definition of MetS (Table 2). Age was also associated with MetS in the women population with a current MDE. When including the number of previous MDE instead of MDD duration in the model, results did not change. The values of the OR were 2.4 (95%CI (1.4–4.1), $p = 0.002$) and 1.9 (95% CI (1.1–3.1), $p = 0.01$) when using NCEP ATP III or IDF definitions for MetS, respectively (data not shown). A supplementary analysis including an interaction variable of age and insomnia (Age*insomnia) has been performed. This variable was not associated with MetS ($p > 0.1$ and $p > 0.3$ for NCEP ATP III and IDF, respectively).

In women aged ≥50years, results were similar than in the whole women subpopulation. In multivariate logistic regressions controlled for age, current smoking, educational level, diabetes status and MDD duration, severe insomnia was related to metabolic syndrome, with OR values of 2.6 (95%CI (1.3–5.4)) and 2.2 (95%CI (1.3–4.2)) for NCEP ATP III and IDF definitions, respectively (Table 2). The same analyses conducted in women younger than 50 years did not find any association between severe insomnia and MetS.

3.4. Association of insomnia and MetS in men

We did not find any significant association between severe insomnia and MetS in the men population (data not shown).

4. Discussion

Main results and literature comparison: the main result of this study is that there is a positive association between insomnia and MetS prevalence in depressed women MDE but not in depressed men. This result is independent from age, current tobacco smoking, education level and MDD duration or number of previous MDE. In women with severe insomnia, with the NCEP ATP III criteria, the prevalence of MetS was approximately two-fold higher than in women with no severe insomnia. Because age could influence sleep (Mander et al., 2017), we included an interaction variable in a supplementary model (Age*insomnia). This variable was not associated with MetS.

Regarding women with severe insomnia, we observed a prevalence of MetS from 25% (NCEP ATP III) to 31% (IDF). This is higher than the French general population (with no gender consideration) of 14.1% (NCEP ATP III) to 20.3% (IDF) (Vernay et al., 2013) and broadly higher than the French general women subpopulation (aged 40–64 years) of the D.E.S.I.R. study which found a 10% prevalence of MetS by using NCEP ATP III definition Balkau et al., (2003). Of note, this is approximately the prevalence we found in women without severe insomnia (14% when using NCEP ATP III) (Table 1). These results thereby reinforce the association between MetS and severe insomnia in women with a current MDE.

Because menopausal status is widely associated with change in metabolism, and especially in the prevalence of metabolic syndrome in women (Marchi et al., 2017) we conducted a supplementary analysis with the cut-off of being 50 years, which is the cut-off age for menopausal status in women. We showed, that the association between severe insomnia and MetS only remained who were 50 years old or older. This is very interesting because result of Women's Health Initiative

Table 2
Bivariate and multivariate logistic regressions for the association of MetS and severe insomnia.

Bivariate model	WHOLE POPULATION (n = 624)		MetS IDF		WOMEN SAMPLE (n = 433)		MetS IDF	
	n(%)	p	n(%)	p	n(%)	p	n(%)	p
Severe Insomnia	83(25)	0.1	99(32)	0.3	59(25)	0.008	72(31)	
No Severe insomnia	56(19)		75(24)		29(14)		43(22)	
Multivariate models	OR [95%CI]	P	OR [95%CI]	P	OR [95%CI]	P	OR [95%CI]	P
Severe Insomnia	1.4[0.9–2.1]	0.1	1.2 [0.8–1.8]	0.4	2.2 [1.3–3.9]	0.004	1.8 [1.1–2.9]	
Age	1.04 [1.02–1.06]	<0.0005	1.05 [1.03–1.07]	<0.0005	1.02 [1.03–1.08]	<0.0005	1.06 [1.04–1.09]	
Education level	0.8 [0.6–1.03]	0.07	0.8 [0.6–1.0]	0.08	0.8 [0.5–1.1]	0.2	0.7[0.5–1.1]	
MDD duration	1.0 [0.98–1.02]	0.8	1.0 [0.98–1.01]	0.9	1.0 [0.98–1.03]	0.5	1.0 [0.98–1.02]	
Current smoking	1.1[0.7–1.8]	0.5	1.1 [0.7–1.6]	0.7	1.6 [0.9–2.8]	0.1	1.6 [0.9–2.7]	
Diabetes status	6.6 [3.2–13.5]	<0.0005	4.9 [2.4–10.2]	<0.0005	10.1 [4.0–25.5]	<0.0005	7.5 [2.9–17.4]	
Sex (reference Men)	0.7 [0.4–1.1]	0.1	0.8 [0.5–1.2]	0.4				
WOMEN < 50 (n = 248)								
MetS NCEP ATP III		MetS IDF		MetS NCEP ATP III		MetS IDF		
n(%)	p	n(%)	p	n(%)	p	n(%)	p	
18(14)	0.2	23(17)	0.4	41(40)	0.01	49(48)	0.03	
10(9)		16(7)		19(23)		27(32)		
Multivariate models	OR [95%CI]	P	OR [95%CI]	P	OR [95%CI]	P	OR [95%CI]	P
1.7[0.7–4.1]	0.2	1.3[0.6–2.8]	0.5	2.6[1.3–5.4]	0.009	2.2[1.3–4.2]	0.02	
1.06[1.00–1.11]	0.04	1.08[1.02–1.13]	0.004	1.0[0.95–1.07]	0.7	1.05[0.99–1.11]	0.07	
0.6[0.3–1.2]	0.2	0.6[0.3–1.2]	0.1	0.9[0.5–1.6]	0.7	0.8[0.5–1.3]	0.3	
0.9[0.9–1.0]	0.5	0.9[0.9–1.0]	0.3	1.0[0.99–1.04]	0.3	1.0[0.99–1.03]	0.4	
2.5[1.0–6.1]	0.04	2.3[1.1–5.1]	0.03	1.05[0.5–2.4]	0.9	1.05[0.9–2.3]	0.9	
11.6[2.8–48.6]	0.001	21.0[4.6–96.0]	<0.0005	11.3[3.2–39.6]	<0.0005	4.03[1.3–12.7]	<0.0005	
WOMEN > 50 (n = 185)								
MetS NCEP ATP III		MetS IDF		MetS NCEP ATP III		MetS IDF		
n(%)	p	n(%)	p	n(%)	p	n(%)	p	
18(14)	0.2	23(17)	0.4	41(40)	0.01	49(48)	0.03	
10(9)		16(7)		19(23)		27(32)		
Multivariate models	OR [95%CI]	P	OR [95%CI]	P	OR [95%CI]	P	OR [95%CI]	P
1.7[0.7–4.1]	0.2	1.3[0.6–2.8]	0.5	2.6[1.3–5.4]	0.009	2.2[1.3–4.2]	0.02	
1.06[1.00–1.11]	0.04	1.08[1.02–1.13]	0.004	1.0[0.95–1.07]	0.7	1.05[0.99–1.11]	0.07	
0.6[0.3–1.2]	0.2	0.6[0.3–1.2]	0.1	0.9[0.5–1.6]	0.7	0.8[0.5–1.3]	0.3	
0.9[0.9–1.0]	0.5	0.9[0.9–1.0]	0.3	1.0[0.99–1.04]	0.3	1.0[0.99–1.03]	0.4	
2.5[1.0–6.1]	0.04	2.3[1.1–5.1]	0.03	1.05[0.5–2.4]	0.9	1.05[0.9–2.3]	0.9	
11.6[2.8–48.6]	0.001	21.0[4.6–96.0]	<0.0005	11.3[3.2–39.6]	<0.0005	4.03[1.3–12.7]	<0.0005	

Abbreviations: MetS: Metabolic Syndrome, IDF: criteria for International Diabetes Federation, NCEP ATP III: criteria for National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).

found an association between sleep duration (and insomnia) with cardiovascular disease event and coronary heart disease in the general population of women ($n = 86,329$) with an age between 50–79 years (Sands-Lincoln et al., 2013). These results are also showed in a Chinese population of 154 post-menopausal women, where poor sleep quality (measured by the Pittsburgh Sleep Quality index) was related to a 10 years elevation of cardiovascular risk measured by the Framingham 10-year risk score (Chair et al., 2017). Although there are many other reports of this association, our study is the first study which showed that severe insomnia is associated with MetS in the MDD during MDE, and also that this is a specificity of the subgroup of women aged ≥ 50 years compared to women aged < 50 years. This finding could be due to decrease in estrogens during ageing in women. Indeed, the decrease in estrogens during menopause could be linked with a lower sleep quality (Carrier et al., 2017) and also with an increase of cardiovascular risk in women Merz and Cheng, (2016). Considering MDD, a previous study assessed in 905 young adults ($25.81 \text{ years} \pm 2.18$) with a current MDE, the relation between circadian disorders (assessed by the BRIAN scale) and MetS (NCEP ATP III) Moreira et al., (2016). They found an association of sleep and social domains of the BRIAN scale with MetS during MDE in young adults. However, they did not assess sex differences neither insomnia specifically. Considering sex specificity, St-Onge et al. studied a small sample of 27 healthy men and women under short (4 h) or normal (9 h) sleep conditions for 4 days (St-Onge et al., 2012). They found Glucagon-like peptin-1 (GLP-1), a peptide involved in satiety, to be decreased only in the female subgroup of short-sleep. Contrariwise, total ghrelin levels were increased in the subgroup of short sleep men with but not in women. These findings suggest a sex specific hormonal effect on metabolism during sleep variation. Moreover, it has been shown that sleep deprivation or short sleeping lead to a sex-specific response in daily food intake and weight gain (Markwald et al., 2013; Dashti et al., 2015).

In men, we did not find any difference in this prevalence between groups (Table 2). Usually, MetS is significantly more prevalent in men subgroups of the general population before 50 years than in women and the ratio changes later (Pucci et al., 2017). In our sample, the mean age is close to 50, so this is not surprising, but nonetheless it is interesting that we found no difference between sexes. The reason of this observation deserves further investigation.

Limits: However, several limits have to be considered. Firstly, we used clinician-rated insomnia even though recommendations argue for using sleep electroencephalography and actimetry (Zhang and Zhao, 2007). Indeed, there is some discrepancies between objective and subjective sleep measures (Orff et al., 2007; Rezaie et al., 2018). Nevertheless, objective measures of sleep are not currently used in standard practice. Hence, our results are in phase with the real-life assessment of patients by clinicians and could be efficient in targeting patients. Secondly, the sleep apnea syndrome has not been neither assessed. It's worthy to note that insomnia and sleep apnea syndrome frequently co-occur (Luyster et al., 2010) but it could not be known if it was in the METADAP cohort. Sleep apnea syndrome is highly associated with MetS (Xu et al., 2015). Thus, it would have been useful to add sleep apnea syndrome has a covariate in multivariate analyses. Moreover, although not exclusive, abdominal obesity (a central criterion of MetS) is a key risk factor for sleep apnea syndrome (Li et al., 2018), and insomnia is a known factor for metabolic dysregulation (Deng et al., 2017). Thus, it could be a bilateral association in which insomnia leads to MetS, which in turn can promote insomnia. Moreover, MDD is also a risk factor for MetS (Penninx et al., 2013; Penninx, 2016). Indeed, understanding the direction of the association between insomnia and MetS remains an unsolved challenge.

Thirdly, some variables such as alcohol consumption, benzodiazepines intake, previous antidepressant prescription and the past history of coronary heart disease were not assessed but could be associated with insomnia and MetS.

Fourthly, the size of the women sample ($n = 433$) is larger the size

of the men sample ($n = 191$). This difference could be the reason why we did not reach to find any difference in men. However, we did not detect any difference in the whole sample ($n = 624$) and the interaction model found that the insomnia*sex variable to be significant to explain MetS prevalence.

Finally, we did not check for the menopausal status of women which is a known variable linked to metabolism change and cardio-vascular risk (Auro et al., 2014). Moreover, menopausal status is linked with obstructive sleep apnea (Eichling and Sahni, 2005). However, we conducted a supplementary analysis in which we selected women aged ≥ 50 years, because this age is considered as a cut-off for menopausal transition (Sherman, 2005). Moreover, women younger than 50 years did not show this association.

To conclude, this study confirms and goes further our previous results (Costemale-Lacoste et al., 2017). Women aged ≥ 50 years with a severe insomnia during MDE have an increased risk of MetS. Severe insomnia may be a clinical marker of metabolic risk in women aged ≥ 50 years with major depression. They should be particularly monitored for MetS and may benefit from sleep recommendations and cardiovascular prevention.

Authors statement

Jean-François Costemale-Lacoste is the main author of the manuscript (writing and statistics)

Khalil El Asmar has served as a writer and advisor for its knowledge on statistics

Adrien Rigal has served as writer and for its knowledge and interest on metabolism in mood disorders

Séverine Martin has served as writer and for its knowledge and interest on metabolism in mood disorders

Abdel Kader Ait Taieb has served as a reviewer and advisor on clinical data

Romain Colle has served as reviewer and advisor for its knowledge on clinical research

Laurent Becquemont was the head of the clinical research center in CHU Le Kremlin-Bicêtre and reviewed the article

Bruno Fève has served as a reviewer of the entire manuscript and as an advisor for its knowledge in endocrinology and metabolism

Emmanuelle Corruble is the head of the “depression and antidepressants” team, she conducted and supervised the METADAP Study, she's the main investigator of METADAP study

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Declaration of Competing Interest

None.

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