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ABSTRACT:

Aims: Depression is associated with increased risk of cardiovascular disease and the role of poor medical adherence is mostly unknown. We studied the association between depressive symptoms and non-adherence to medications targeting treatable cardiovascular risk factors in the CONSTANCES population-based French cohort.

Methods and Results: We used CONSTANCES data linked to the French national healthcare database to study the prospective association between depressive symptoms (assessed at inclusion with the Center for Epidemiological Studies Depression scale) and non-adherence to medications (less than 80% of trimesters with at least one drug dispensed) treating type 2 diabetes, hypertension and dyslipidaemia over 36 months of follow-up. Binary logistic regression models were adjusted for socio-demographics, body mass index and personal history of cardiovascular disease at inclusion. Among 4,998 individuals with hypertension, 793 with diabetes and 3,692 with dyslipidaemia at baseline, respectively 13.1% vs. 11.5%, 10.5% vs. 5.8% and 29.0% vs. 27.1% of those depressed versus those non-depressed were non-adherent over the first 18 months of follow-up (15.9% versus 13.6%, 11.1% vs. 7.4% and 34.8%vs. 36.6% between 19-36 months). Adjusting for all covariates, depressive symptoms were neither associated with non-adherence to medications for hypertension, diabetes and dyslipidaemia over the first 18 months of follow-up, nor afterwards. Depressive symptoms were only associated with non-adherence to anti-diabetic medications between the first 3-6 months of follow-up.

Conclusion: Non-adherence to medications targeting treatable cardiovascular risk factors is unlikely to explain much of the association between depressive symptoms and CVD at a population level. Clinicians are urged to search for and treat depression in individuals with diabetes to foster medications adherence. **Keywords:** depressive symptoms; hypertension; diabetes; dyslipidaemia; medication; adherence

INTRODUCTION

Depression is not only one of leading causes of disability worldwide, but it has been repeatedly associated with cardiovascular disease (CVD) [1, 2]. In addition, cardiovascular risk factors are highly prevalent in the presence of depression [3-5]. The association between depression and CVD could thus be partially explained by poor adherence to medications regarding treatable cardiovascular risk factors, namely hypertension, diabetes mellitus and dyslipidaemia. The prevalence of non-adherence to medications in chronic diseases, including hypertension, diabetes and dyslipidaemia [6], is estimated to be 50% in developed countries [7]. Moreover, around 20% of newly prescribed medications are never filled, and around 50% of those that are filled are not taken correctly in terms of frequency, dosage, duration and timing [8]. As hypertension, diabetes, and hypercholesterolemia contribute to 68% of all deaths worldwide [6], improving adherence to medications treating these conditions is a critical challenge for public health [9, 10]. This challenge might be even more critical in individuals with depression.

Overall, depression has been associated with poor adherence to medications in various settings [11]. A recent meta-analysis showed that depressed patients are 1.76 times more likely to be non-adherent to chronic disease medications compared to their non-depressed counterparts. Specifically, the adjusted odds ratios (OR) of being non-adherent among depressed patients are 1.73 (95% confidence interval (CI): 1.24-2.87) and 1.79 (95% CI: 1.28-2.51) compared to non-depressed patients in six studies on diabetes and eight studies on hypertension or dyslipidaemia, respectively [11]. However, adjustment variables differ from one study to the other and residual confounding could not be excluded. In addition, most of these studies were conducted in clinical samples and evidence from the general population is sparse. To our knowledge, eight studies assessed these associations using population-based samples, but only three were prospective studies using objective measures of treatment adherence [12-14] and none of these three studies assessed hypertension, diabetes, and hypercholesterolemia jointly.

Taking advantage of a population-based cohort study linked to administrative claim database, we aimed to examine the prospective association between depressive symptoms and subsequent non-adherence to medications each targeting hypertension, diabetes type 2 and dyslipidaemia in a large-scale, diverse adult population living in France.

METHODS

Study Design

The CONSTANCES cohort is a large population-based study of 18-69 years old volunteers randomly selected from 22 health-screening centres (HSCs) in different districts across France since 2012 that reached 200,000 participants by early 2019 [15]. These volunteers were covered by the French national health insurance fund; hence, this study covered 85% of the adult population in France and excluded self-employers, farmers and undocumented immigrants. Volunteers were asked at inclusion to complete self-administrated questionnaires by mail on lifestyle and socio-demographic characteristics as well as socio-professional and health statuses. Additionally, they underwent health examination such as laboratory tests and physical examination in the HSCs. If a new disease was discovered after the full assessment, including hypertension, diabetes and dyslipidaemia, the participants were informed and offered a medical consultation to review their results with the HSC physicians.

Participants' data were matched to the 'Système National d'Information Interrégimes de l'Assurance Maladie' (SNIIRAM) database through specific identifiers. This database included information on all reimbursed medications [16], which served to identify the use and adherence to pharmacological treatments targeting several diseases including cardiovascular risk factors such as hypertension, diabetes and dyslipidaemia from January 1, 2009 to December 31, 2017.

The CONSTANCES cohort received authorization from regulatory bodies supervising medical research in France which are the 'Commission de l'Informatique et des Libertés - CNIL' (authorization no. 910486), the Institutional Review Board of the National Institute for Medical Research-INSERM, the 'Conseil National de l'Ordre des Médecins - CNOM' and 'Conseil National de l'Information Statistique - CNIS' [15].

Study populations

We first defined the presence of hypertension, diabetes type 2 and dyslipidaemia by either self-reports in the medical questionnaire administrated by the physician at inclusion, or abnormal blood pressure/ blood tests on the medical examination offered at study inclusion, or both. Abnormal blood pressure was defined as a systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg. Abnormal glycaemia, cholesterol, triglycerides levels were defined as fasting glucose ≥7 mmol/l, fasting LDL-cholesterol >4.08 mmol/l and/or fasting triglycerides ≥1.7 mmol/l respectively. Blood

pressure and blood tests were collected from laboratory tests at inclusion during the visit to the HSCs based on standardized procedures [17]. For instance, blood pressure was measured using oscillometric sphygmomanometer based after 5 minutes of rest. The blood tests were collected and pre-treated within a maximum of 30 minutes period, then transported to the central laboratory on the same day at 4-8 degrees [15].

A total of 151,207 participants were enrolled in CONSTANCES between February 2012 and March 1, 2018. Among them, 128,700 had available SNIIRAM data and 45,052 were included before January 1, 2015, thus having 36 months of follow-up (**Supplemental Figure 1**). Among these 45,052 individuals, we included individuals with the condition under study (i.e. either hypertension, diabetes or dyslipidaemia), who had at least one drug prescriptions filled in the 6 months before inclusion and who completed the Center for Epidemiologic Studies Depression (CES-D) scale at inclusion. Since our primary outcome was medication non-adherence at follow-up, being on medication on the day of inclusion was not required as inclusion criteria. Information on date of drug prescriptions filled was collected from the SNIIRAM database. Pharmacological treatment of the conditions under study was identified according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification [18].

Assessment of depressive symptoms

Depressive symptoms were assessed at baseline using the French version of the CES-D scale [19]. The CES-D scale is composed of 20 items that assess depressive symptoms in the past week such as agitation, guilt, loss of appetite and interest, fatigue, suicidal thoughts and sadness (e.g. I felt sad, I felt lonely) on a scale from 0-3 with 0 being 'rarely' (<1 day) and 3 'most of the time' (5 to 7 days). Internal consistency of CES-D scale is generally high ($\alpha = 0.90$ in the CONSTANCES cohort). Volunteers with a score of ≥19 were considered to be clinically depressed according to the validated threshold for the French version (sensitivity and specificity >85% for the diagnosis of major depression) [19]. However, to incorporate volunteers with more severe depressive symptoms for minimizing type I error, sensitivity analyses were performed with the CES-D score using two thresholds with higher specificity: 21 (sensitivity 82%, specificity 91%) and 22 (sensitivity 79%, specificity 92%) [19].

Assessment of non-adherence to medications

Non-adherence to cardiovascular risk factors' medications under study was assessed by tracking the reimbursement of ad hoc medications over 18 months after the date of inclusion and 18 months afterwards (19-36 months). To measure medication non-adherence, we divided the sum of trimesters with at least one drug dispensed by the total number of trimesters (i.e. 6 trimesters) [20] (**Supplemental Equation 1**). Participants were considered non-adherent if they purchased the studied drugs less than 80% of time, a commonly used threshold in studies of medication non-adherence [20]. In addition, exploratory analyses were performed using medication non-adherence between the first 3-6 months after the date of inclusion (i.e. had at least one trimester without drug dispensed) to test whether non-adherence to medications would be more sensitive to depressive symptoms in this period.

Assessment of covariates

Age (continuous, years), sex, living with a partner (yes; no), country of birth (France; other), educational level (≤ high school diploma: ≤13 years of education; undergraduate degree: between 14 and 16 years of education; postgraduate degree: ≥17 years of education) and employment status (yes; no) were collected at inclusion from volunteers' self-reports. Physical activity (0: not active to 6: very active) and prescribed and followed diet (yes; no) at inclusion were also collected from the same source for descriptive purpose. Personal history of CVD (yes: history of angina pectoris, myocardial infarction, stroke or peripheral arterial diseases; no) was collected from the medical questionnaires administrated by the physician at inclusion. Body mass index, BMI (<25; ≥25 and <30; ≥30 kg/m^2) was calculated at inclusion.

Statistical analysis

All analyses were conducted using the SAS system software (version 9.4, SAS Institute, Cary, NC). Independent t-tests, Chi-Square tests and Fisher's exact tests were computed for demographic and clinical characteristics by the presence of depressive symptoms. First, as our primary analyses, the associations between depressive symptoms at inclusion and non-adherence to medications treating hypertension, diabetes or dyslipidaemia either in the first 18 months or between 19 and 36 months of follow-up were studied with unadjusted and fully-adjusted logistic regression models. Based on an anticipated rate of non-adherence of 25% in this sample of individuals presumably more health-

conscious than the general population, an anticipated rate of 20% of participants with depressive symptoms (i.e. a CES-D score >19) and an anticipated Odds-Ratio of 1.75 for non-adherence in the presence of depressive symptoms [11], we calculated that a minimum of 706 participants would be needed for a given condition to achieve a statistical power of 80% with an alpha risk set at 5% [21]. This sample size was corresponding to the expected sample size of participants with diabetes, with larger samples being expected for participants with hypertension or dyslipidaemia. Fully-adjusted models were adjusted for all the covariates mentioned above, except for prescribed diet and physical activity. These two variables were excluded since they could be part of the non-pharmacological treatment of the condition, thus capturing a part of medical adherence. In other words, adjusting for these variables may result in an artificial underestimation of the association of depressive symptoms with medication non-adherence. Second, as exploratory analyses, these analyses were repeated between the first 3-6 months to explore whether non-adherence to medications would be more sensitive to depressive symptoms in this period.

Since socio-demographics (i.e. age, sex and educational level) may be effect modifiers of the association between depressive symptoms and non-adherence to medications, we tested for statistical interactions between depressive symptoms and these variables. Should these interactions be significant, we planned to further examine the association between depressive symptoms and non-adherence to medications in stratified analyses.

All analyses were computed using multiple imputations to handle missing values in the covariates.

RESULTS

The characteristics of participants with hypertension (N=4,998), diabetes (N=793) and dyslipidaemia (N=3,692) are presented in **Table 1**. The overlap between the three populations under study is displayed in **Supplemental Figure 2**. The prevalence of depressive symptoms varied from 16.2% in individuals with dyslipidaemia to 21.8% in those with diabetes. The majority of study participants were men, living with a partner, French by birth, non-employed, physically active, had a high school diploma at best and a BMI between 25 and 30, did not follow a prescribed diet, did not have a personal history of CVD. Over the first 18 months of follow-up, 0.2% of individuals with

hypertension, 0.4% with diabetes and 0.1% with dyslipidaemia died and thus were not included in the subsequent analyses as well as 0.9%, 1.4% and 0.4% between 19-36 months.

Among individuals with hypertension, diabetes and dyslipidaemia, respectively 13.1% vs. 11.5%, 10.5% vs. 5.8% and 29.0% vs. 27.1% of those with vs. without depressive symptoms were non-adherent (i.e. had a proportion of trimesters with at least one drug dispensed of <80%) over the first 18 months of follow-up, and15.9% vs. 13.6%, 11.1% vs. 7.4% and 34.8% vs. 36.6% between 19-36 months.

Among participants with diabetes, hypertension or dyslipidaemia, depressive symptoms were neither associated with non-adherence to medications over the first 18 months of follow-up, nor afterwards (**Table 2**). Similar findings were obtained in the fully adjusted models while using CES-D thresholds of 21 and 22 (**Supplemental Tables 1 and 2**). None of the interactions between depressive symptoms and socio-demographic variables were significant (all $P \geq 0.06$); hence, we did not further stratify our analyses according to these variables. However, in the exploratory analyses, depressive symptoms became associated with non-adherence to anti-diabetic medications between the first 3-6 months of follow-up with ORs ranging from 2.40- 2.80 whatever the CES-D score threshold (**Supplemental Table 3**).

DISCUSSION

This study aimed to examine the prospective association between depressive symptoms, and non-adherence to medications for treatable major cardiovascular risk factors, namely hypertension, diabetes type 2, and dyslipidaemia, in a population-based setting. Overall, the results suggest that depressive symptoms were neither associated with non-adherence to medications for hypertension, diabetes, and dyslipidaemia over the first 18 months, nor afterwards. However, depression might be associated with non-adherence to antidiabetic medications for diabetes between the first 3-6 months.

There were certain strengths in this study. First, to our knowledge, this is the first study that examines the association between depressive symptoms and non-adherence to medications targeting the three main treatable cardiovascular risk factors in a single prospective, population-based cohort using administrative claim databases rather self-reported adherence. Second, the systematic linkage between a national population-based cohort and a national healthcare administrative database offered the opportunity to use actual prescriptions filled as dependent variable with no loss to follow-up while

considering several potential confounders or effect modifiers. Overall, except for educational level, the significant associations of these potential confounders with non-adherence to medications were somehow consistent with those found in the literature [22-25]. Third, the clinical and laboratory data were collected according to standardized procedures by specialized teams at health-screening centres [17]. Fourth, because the results of these procedures were disclosed to the participants, non-adherence is unlikely to be explained by a lack of awareness of the disease.

However, this study had also limitations, mainly resulting from the characteristics of the SNIIRAM database. First, this database does not provide detailed information on the conditions warranting the prescription of medications. For instance, some anti-diabetic medications may have been prescribed to lose weight [26]. Second, the SNIIRAM database does not contain information about actual medication use. However, it is unlikely that patients with regularly filled prescriptions did not take their medication at all. Third, detailed information about non-pharmacological treatments is not available in this database. For instance, participants who did not take pharmacological treatment were considered to be non-adherent, although some of them were possibly prescribed non-pharmacological treatments (e.g. change in diet, increased physical activity) only [27, 28]. Fourth, although the CONSTANCES cohort is a large community-based population in France, with a broad socio-demographic diversity, the majority had a favourable social context. In addition, the prevalence of the conditions was lower than expected from the general population and this could be explained by the fact that CONSTANCES participants are more interested in their health. However, the low prevalence of diabetes is a very common phenomenon in any cohort [29] where individuals with diabetes are typically less prone to participate than to those with hypertension and dyslipidaemia. Furthermore, we showed that socio-demographics were not significant effect modifiers, thus limiting the risk of our results to be affected by selection biases. Fifth, the CES-D scale measures self-reported depressive symptoms and not major depression. For instance, functional impairment because of depressive symptoms is a diagnostic criterion of major depression that is not assessed by the CES-D. However, the association between depression and increased risk of CVD is not specific to major depression but also observed for subthreshold depressive symptoms. Our hypothesis was therefore that current depressive symptoms could impede medication adherence. However, since these symptoms were assessed only once at baseline, they may reflect a transient state that was not present later during follow-up. Sixth, we did not take into account antidepressant medications because, as stated above,

our hypothesis was about current depressive symptoms and antidepressants per se were not supposed to have a direct effect on medication adherence. In addition, data from the French national health insurance system suggest that antidepressant drugs are frequently prescribed for reasons other than depression (i.e. migraine) [30]. Finally, although the broader hypothesis we aimed to test was whether medications adherence to treatable cardiovascular risk factors could be a potential mediator of the association between depressive symptoms and cardiovascular disease, the present study only tested a part of this hypothesis.

The lack of association between depressive symptoms and non-adherence to medications for hypertension or dyslipidaemia in the participants concerned was not in line with our hypothesis. This lack of association was indeed consistent with the results of some previous studies [31-33] but not with others [34-38] for hypertension. It was also not in line with the results of one study for dyslipidaemia [39]; however, the authors did not assess depressive symptoms by themselves: they combined it with anxiety. Overall, these studies were either retrospective [32, 40] or prospective with a follow-up period of 2 years at best. Furthermore, only three studies [12-14] used prospective population-based cohorts to assess the medication adherence based on objective measures. These three studies showed a positive association between depressive symptoms and non-adherence to medications over time. However, the first study measured non-persistence rather than non-adherence [13]. The second study assessed non-adherence to medications targeting various cardio-metabolic conditions among adults with diabetes [12] and the third one used either depressive symptoms or anxiety as independent variable among old adults with hypertension [14].

In contrast, the lack of a significant association between depressive symptoms and non-adherence to medications in individuals with diabetes in our primary analyses is more difficult to reconcile with the literature [41-47]. Only two studies [48, 49] showed no association between these two variables and mainly when medication adherence was assessed using electronic caps [49]. However, most studies linking depression with non-adherence to anti-diabetic medication were either retrospective studies [41-43] or prospective with only one timepoint at follow-up. Indeed, depressive symptoms were associated with an almost two-time higher odd of being non-adherent to anti-diabetic medications in the first 18 months, whereas the OR was close to one for antihypertensive or lipid lowering medications. However, compared to hypertension and dyslipidaemia, our study might have lacked statistical power for diabetes because of the lower than expected proportion of those being non-

adherent to anti-diabetic medications (i.e. 7% instead of 25%). This proportion would have required a 50% larger sample to achieve a statistical power of 80% [21]. Compared to hypertension and dyslipidaemia, the treatment for controlling diabetes is by far more demanding for patients, as they have not only to implement both pharmacological and non-pharmacological treatments, but also to monitor the condition several times a day, as well as being aware of possible acute complications of both the disease (e.g. ketoacidosis) and treatment (e.g. hypoglycaemia) and to be prepared to manage them in first line; hence depressive symptoms have more room to eventually interfere with medication adherence. Finally, the effect of a potential association between depressive symptoms at inclusion and non-adherence to anti-diabetic medication may have reduced after 18 months of follow-up because depressive symptoms are a potentially transient state rather than a permanent trait. In support to this hypothesis, exploratory analyses showed that depressive symptoms were associated with non-adherence to anti-diabetic medications between the first 3-6 months of follow-up only. Hence, further studies may consider depressive symptoms as time-dependent variables to examine this hypothesis. Specifically, repeated measures of depressive symptoms would allow testing the hypothesis of a detrimental effect of depressive symptoms on adherence to anti-diabetic medications – or other demanding treatment –in the short run only with a within-individual approach. In addition, studies that would rely on data gathered in the general population rather in volunteers only are needed to provide more definitive conclusions regarding the lack of association between depressive symptoms and adherence to medications for hypertension or dyslipidaemia.

In conclusion, in a population-based cohort, depressive symptoms were not associated with non-adherence to medications for hypertension, diabetes and dyslipidaemia in primary analyses. Although we may have lacked power for anti-diabetic medications, our results suggest that non-adherence to medications targeting treatable cardiovascular risk factors is unlikely to explain much of the association between depressive symptoms and CVD incidence. Although this association has been established for years, ruling out the hypothesis of a mediation by medication non-adherence is critical for depressive symptoms to be considered as CVD risk factor on its own [2]. Our finding suggests that other pathways (i.e. pathophysiological pathways) should be further explored to understand this association and identify relevant targets for preventive strategies. For example, depressive symptoms could lead to autonomic dysregulation triggering increased risk of CVD as the cortisol levels are high in depressed individuals and they are associated with CVD outcomes [50]. However, exploratory results

suggest that depressive symptoms may be associated with anti-diabetic medications non-adherence in the short run. Although this finding warrant replication, it suggests that searching and treating depression may be especially important in individuals with diabetes as it may contribute to foster medications adherence. Future studies based on repeated measures of depressive symptoms and adherence in larger samples may further test this hypothesis.

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References

1. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. Eur Heart J 2006;**27**(23):2763-74.
2. Hamieh N, Meneton P, Wiernik E, Limosin F, Zins M, Goldberg M, Melchior M, Lemogne C. Depression, treatable cardiovascular risk factors and incident cardiac events in the Gazel cohort. Int J Cardiol 2019;**284**:90-95.
3. Meng L, Chen D, Yang Y, Zheng Y, Hui R. Depression increases the risk of hypertension incidence: a meta-analysis of prospective cohort studies. J Hypertens 2012;**30**(5):842-51.
4. Yu M, Zhang X, Lu F, Fang L. Depression and Risk for Diabetes: A Meta-Analysis. Can J Diabetes 2015;**39**(4):266-72.
5. Olusi SO, Fido AA. Serum lipid concentrations in patients with major depressive disorder. Biol Psychiatry 1996;**40**(11):1128-31.
6. World Health Organization. Global Status Report on Noncommunicable Diseases. In; 2014, 298.
7. World Health Organization. Adherence to long-term therapies: Evidence for action. In; 2003.
8. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;**353**(5):487-97.
9. Ting HH, Shojania KG, Montori VM, Bradley EH. Quality improvement: science and action. Circulation 2009;**119**(14):1962-74.
10. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care 2004;**42**(3):200-9.
11. Grenard JL, Munjas BA, Adams JL, Suttorp M, Maglione M, McGlynn EA, Gellad WF. Depression and medication adherence in the treatment of chronic diseases in the United States: a meta-analysis. J Gen Intern Med 2011;**26**(10):1175-82.
12. Bauer AM, Parker MM, Moffet HH, Schillinger D, Adler NE, Adams AS, Schmittdiel JA, Katon WJ, Karter AJ. Depressive symptoms and adherence to cardiometabolic therapies across phases of treatment among adults with diabetes: the Diabetes Study of Northern California (DISTANCE). Patient Prefer Adherence 2017;**11**:643-652.
13. Sjosten N, Nabi H, Westerlund H, Salo P, Oksanen T, Pentti J, Virtanen M, Kivimaki M, Vahtera J. Effect of depression onset on adherence to medication among hypertensive patients: a longitudinal modelling study. J Hypertens 2013;**31**(7):1477-84; discussion 1484.
14. Gentil L, Vasiliadis HM, Preville M, Bosse C, Berbiche D. Association between depressive and anxiety disorders and adherence to antihypertensive medication in community-living elderly adults. J Am Geriatr Soc 2012;**60**(12):2297-301.
15. Zins M, Goldberg M, team C. The French CONSTANCES population-based cohort: design, inclusion and follow-up. Eur J Epidemiol 2015;**30**(12):1317-28.
16. Bezin J, Duong M, Lassalle R, Droz C, Pariente A, Blin P, Moore N. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf 2017;**26**(8):954-962.
17. Ruiz F, Goldberg M, Lemonnier S, Ozguler A, Boos E, Brigand A, Giraud V, Perez T, Roche N, Zins M. High quality standards for a large-scale prospective population-based observational cohort: Constances. BMC Public Health 2016;**16**(1):877.
18. World Health Organization. *ATC/DDD Index 2019*. https://www.whocc.no/atc_ddd_index/.
19. Morin AJ, Moullec G, Maiano C, Layet L, Just JL, Ninot G. Psychometric properties of the Center for Epidemiologic Studies Depression Scale (CES-D) in French clinical and nonclinical adults. Rev Epidemiol Sante Publique 2011;**59**(5):327-40.
20. Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. J Clin Epidemiol 1997;**50**(1):105-16.
21. Demidenko E. Sample size determination for logistic regression revisited. Stat Med 2007;**26**(18):3385-97.
22. Abegaz TM, Shehab A, Gebreyohannes EA, Bhagavathula AS, Elnour AA. Nonadherence to antihypertensive drugs: A systematic review and meta-analysis. Medicine (Baltimore) 2017;**96**(4):e5641.
23. Gupta P, Patel P, Strauch B, Lai FY, Akbarov A, Maresova V, White CMJ, Petrak O, Gulsin GS, Patel V, Rosa J, Cole R, Zelinka T, Holaj R, Kinnell A, Smith PR, Thompson JR, Squire I,

Widimsky J, Jr., Samani NJ, Williams B, Tomaszewski M. Risk Factors for Nonadherence to Antihypertensive Treatment. Hypertension 2017;**69**(6):1113-1120.
24. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. Am J Med 2012;**125**(9):882-7 e1.
25. van der Laan DM, Elders PJM, Boons C, Beckeringh JJ, Nijpels G, Hugtenburg JG. Factors associated with antihypertensive medication non-adherence: a systematic review. J Hum Hypertens 2017;**31**(11):687-694.
26. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, Diabetes Prevention Program Research G. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;**346**(6):393-403.
27. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I. 2018 ESC/ESH Guidelines for the management of arterial hypertension. European Heart Journal 2018;**39**(33):3021-3104.
28. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O, Group ESCSD. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2019.
29. Meneton P, Lemogne C, Herquelot E, Bonenfant S, Larson MG, Vasan RS, Menard J, Goldberg M, Zins M. A Global View of the Relationships between the Main Behavioural and Clinical Cardiovascular Risk Factors in the GAZEL Prospective Cohort. PLoS One 2016;**11**(9):e0162386.
30. Mercier A, Auger-Aubin I, Lebeau JP, Van Royen P, Peremans L. Understanding the prescription of antidepressants: a Qualitative study among French GPs. BMC Fam Pract 2011;**12**:99.
31. Maguire LK, Hughes CM, McElnay JC. Exploring the impact of depressive symptoms and medication beliefs on medication adherence in hypertension--a primary care study. Patient Educ Couns 2008;**73**(2):371-6.
32. Steiner JF, Ho PM, Beaty BL, Dickinson LM, Hanratty R, Zeng C, Tavel HM, Havranek EP, Davidson AJ, Magid DJ, Estacio RO. Sociodemographic and clinical characteristics are not clinically useful predictors of refill adherence in patients with hypertension. Circ Cardiovasc Qual Outcomes 2009;**2**(5):451-7.
33. Wang PS, Bohn RL, Knight E, Glynn RJ, Mogun H, Avorn J. Noncompliance with antihypertensive medications: the impact of depressive symptoms and psychosocial factors. J Gen Intern Med 2002;**17**(7):504-11.
34. Krousel-Wood M, Joyce C, Holt E, Muntner P, Webber LS, Morisky DE, Frohlich ED, Re RN. Predictors of decline in medication adherence: results from the cohort study of medication adherence among older adults. Hypertension 2011;**58**(5):804-10.
35. Forsyth J, Schoenthaler A, Chaplin WF, Ogedegbe G, Ravenell J. Perceived discrimination and medication adherence in black hypertensive patients: the role of stress and depression. Psychosom Med 2014;**76**(3):229-36.
36. Siegel D, Lopez J, Meier J. Antihypertensive medication adherence in the Department of Veterans Affairs. Am J Med 2007;**120**(1):26-32.
37. Bautista LE, Vera-Cala LM, Colombo C, Smith P. Symptoms of depression and anxiety and adherence to antihypertensive medication. Am J Hypertens 2012;**25**(4):505-11.
38. Krousel-Wood M, Islam T, Muntner P, Holt E, Joyce C, Morisky DE, Webber LS, Frohlich ED. Association of depression with antihypertensive medication adherence in older adults: cross-sectional and longitudinal findings from CoSMO. Ann Behav Med 2010;**40**(3):248-57.
39. Stilley CS, Sereika S, Muldoon MF, Ryan CM, Dunbar-Jacob J. Psychological and cognitive function: predictors of adherence with cholesterol lowering treatment. Ann Behav Med 2004;**27**(2): 117-24.
40. Schoenthaler A, Ogedegbe G, Allegrante JP. Self-efficacy mediates the relationship between depressive symptoms and medication adherence among hypertensive African Americans. Health Educ Behav 2009;**36**(1):127-37.
41. Gonzalez JS, Safren SA, Cagliero E, Wexler DJ, Delahanty L, Wittenberg E, Blais MA, Meigs JB, Grant RW. Depression, self-care, and medication adherence in type 2 diabetes: relationships across the full range of symptom severity. Diabetes Care 2007;**30**(9):2222-7.

42. Dirmaier J, Watzke B, Koch U, Schulz H, Lehnert H, Pieper L, Wittchen HU. Diabetes in primary care: prospective associations between depression, nonadherence and glycemic control. Psychother Psychosom 2010;**79**(3):172-8.
43. Raum E, Kramer HU, Ruter G, Rothenbacher D, Rosemann T, Szecsenyi J, Brenner H. Medication non-adherence and poor glycaemic control in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2012;**97**(3):377-84.
44. Gonzalez JS, Safren SA, Delahanty LM, Cagliero E, Wexler DJ, Meigs JB, Grant RW. Symptoms of depression prospectively predict poorer self-care in patients with Type 2 diabetes. Diabet Med 2008;**25**(9):1102-7.
45. Katz LL, Anderson BJ, McKay SV, Izquierdo R, Casey TL, Higgins LA, Wauters A, Hirst K, Nadeau KJ, Group TS. Correlates of Medication Adherence in the TODAY Cohort of Youth With Type 2 Diabetes. Diabetes Care 2016;**39**(11):1956-1962.
46. Lin EH, Katon W, Von Korff M, Rutter C, Simon GE, Oliver M, Ciechanowski P, Ludman EJ, Bush T, Young B. Relationship of depression and diabetes self-care, medication adherence, and preventive care. Diabetes Care 2004;**27**(9):2154-60.
47. Katon W, Russo J, Lin EH, Heckbert SR, Karter AJ, Williams LH, Ciechanowski P, Ludman E, Von Korff M. Diabetes and poor disease control: is comorbid depression associated with poor medication adherence or lack of treatment intensification? Psychosom Med 2009;**71**(9):965-72.
48. Gentil L, Vasiliadis HM, Berbiche D, Preville M. Impact of depression and anxiety disorders on adherence to oral hypoglycemics in older adults with diabetes mellitus in Canada. Eur J Ageing 2017;**14**(2):111-121.
49. Kilbourne AM, Reynolds CF, 3rd, Good CB, Sereika SM, Justice AC, Fine MJ. How does depression influence diabetes medication adherence in older patients? Am J Geriatr Psychiatry 2005;**13**(3):202-10.
50. Tawakol A, Ishai A, Takx RA, Figueroa AL, Ali A, Kaiser Y, Truong QA, Solomon CJ, Calcagno C, Mani V, Tang CY, Mulder WJ, Murrough JW, Hoffmann U, Nahrendorf M, Shin LM, Fayad ZA, Pitman RK. Relation between resting amygdalar activity and cardiovascular events: a longitudinal and cohort study. Lancet 2017;**389**(10071):834-845.

Table 1. Volunteers' characteristics at the inclusion in the CONSTANCES cohort study

	Hypertension	Diabetes	Dyslipidaemia
	N=4,998	N=793	N=3,692
Depressive symptoms*, %	17.5	21.8	16.2
Mean (SD) age, years	60.3 (8.1)	61.0 (7.5)	61.0 (7.5)
Male sex, %	56.7	69.2	61.4
Living with a partner, %	70.3	66.0	70.3
Country of birth (France), %	92.7	86.7	93.6
Educational level			
≤ High school diploma, %	60.9	67.2	61.1
Undergraduate degree, %	25.4	19.8	24.5
Postgraduate degree, %	13.7	13.0	14.4
Employment status, %	38.1	33.5	34.4
Prescribed and followed diet, %	7.0	20.8	7.8
Physical activity			
0 (not active), %	3.3	5.4	3.3
1, %	7.7	10.0	6.4
2, %	18.3	22.9	18.4
3, %	18.4	18.5	18.5
4, %	23.9	21.1	23.2
5, %	13.2	10.7	14.5
6 (very active), %	15.2	11.4	15.7
BMI			
<25, %	27.6	14.0	30.7
≥25 and <30, %	41.8	40.5	44.8
≥30, %	30.6	45.5	24.5
Personal history of CVD, %	11.1	14.0	16.1
Medication non-adherence†			
0-18 months, %	11.9	7.1	27.6
19-36 months, %	14.7	9.2	36.9

*Depressive symptoms were defined as having a CES-D score ≥19.

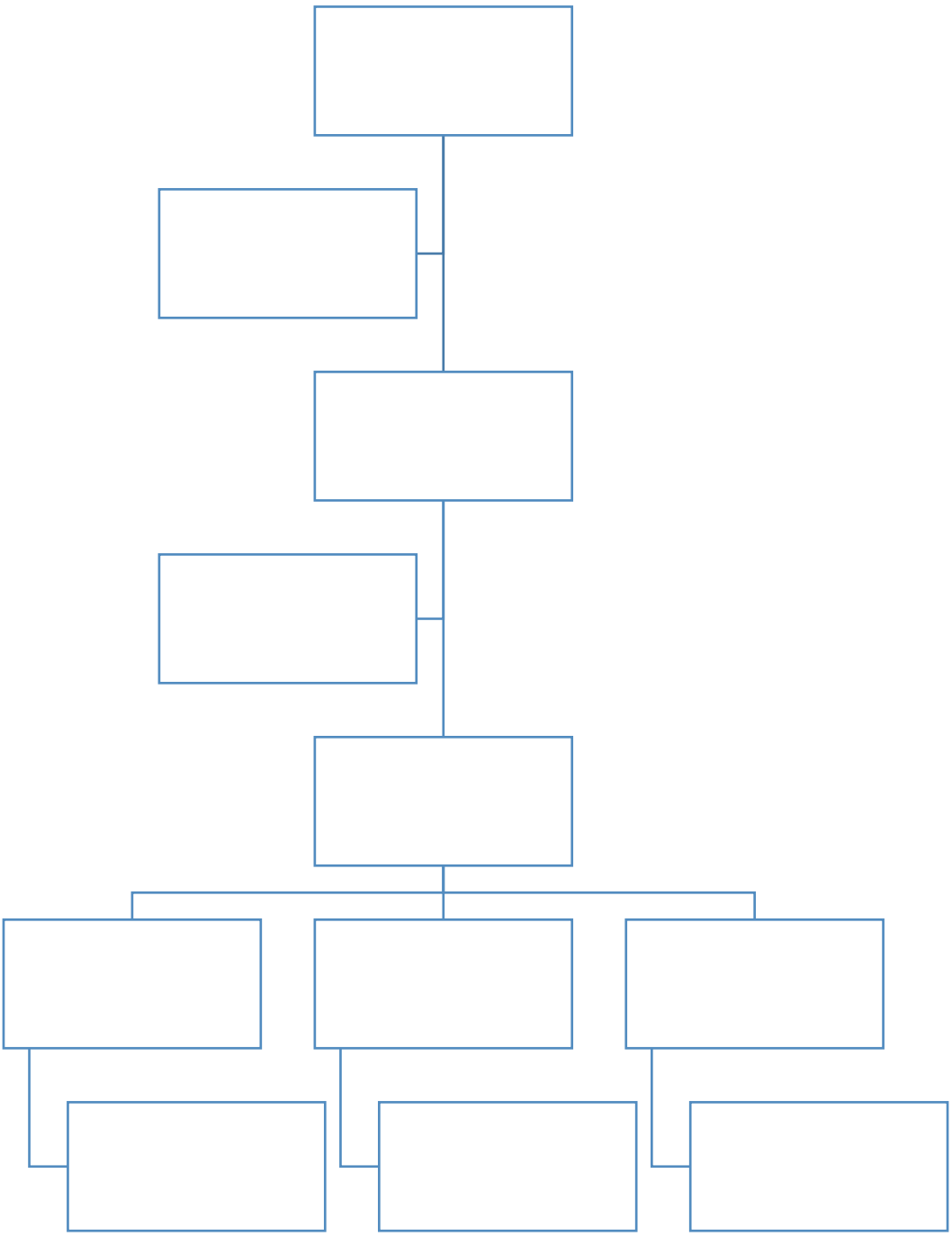
†Non-adherence to medication was defined by a proportion of trimesters with at least one drug dispensed of <80%.

Table 2. Association between depressive symptoms and non-adherence to medications in volunteers with hypertension, diabetes and dyslipidaemia in the CONSTANCES cohort study, according to the duration of exposure to medications, 2012-2018 (odds ratios, ORs and 95% confidence intervals, CI).

	Hypertension			Diabetes			Dyslipidaemia		
	N cases/ N participants	OR (95% CI)	*P*	N cases/ N participants	OR (95% CI)	*P*	N cases/ N participants	OR (95% CI)	*P*
18 months	587/4,987			54/790			1,010/3,681		
Unadjusted model		1.16 (0.93-1.44)	0.18		1.89 (1.04-3.42)	0.03		1.09 (0.90-1.33)	0.36
Fully-adjusted model*		1.08 (0.86-1.36)	0.51		1.82 (0.95-3.48)	0.07		1.04 (0.85-1.28)	0.71
19-36 months	695/4,953			64/782			1,328/3,654		
Unadjusted model		1.19 (0.97-1.46)	0.09		1.22 (0.68-2.20)	0.51		0.92 (0.77-1.11)	0.40
Fully-adjusted model*		1.08 (0.87-1.34)	0.48		1.18 (0.64-2.20)	0.59		0.86 (0.71-1.05)	0.14

* Adjusted for age, sex, living with a partner (yes, no), country of birth (France, other), educational level (≤ high school diploma, undergraduate degree, postgraduate degree), employment status (yes, no), BMI (<25, ≥25 and <30, ≥30) and personal history of CVD (yes, no).

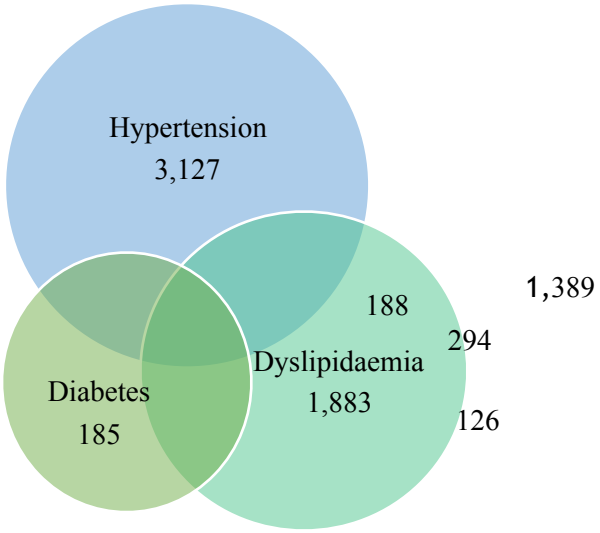
Supplemental Figure 1. Cohort flow chart in the CONSTANCES cohort study



CES-D: The Center for Epidemiologic Studies Depression scale

*Identified by self-reports and/or abnormal blood pressure/blood tests and with at least one drug deliverance in the 6 months before inclusion. Abnormal blood pressure was defined as a systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg. Abnormal glycaemia,

cholesterol, triglycerides levels were defined as fasting glucose ≥7 mmol/l, fasting LDL-cholesterol >4.08 mmol/l and/or fasting triglycerides ≥1.7 mmol/l respectively.



Supplemental Figure 2. Distribution of the conditions in the CONSTANCES cohort study

Supplemental Table 1. Association between depressive symptoms and non-adherence to medications in volunteers with hypertension, diabetes and dyslipidaemia in the CONSTANCES cohort study, according to the duration of exposure to medications, 2012-2018 (odds ratios, ORs and 95% confidence intervals, CI).

	Hypertension			Diabetes			Dyslipidaemia		
	N cases/ N participants	OR (95% CI)	*P*	N cases/ N participants	OR (95% CI)	*P*	N cases/ N participants	OR (95% CI)	*P*
18 months	587/4,987			54/790			1,010/3,681		
Unadjusted model		1.25 (0.99-1.58)	0.053		1.65 (0.87-3.12)	0.12		1.08 (0.87-1.33)	0.48
Fully-adjusted model*		1.17 (0.92-0.20)	0.20		1.59 (0.79-3.19)	0.19		1.03 (0.82-1.29)	0.80
19-36 months	695/4,953			64/782			1,328/3,654		
Unadjusted model		1.24 (0.99-1.53)	0.054		1.28 (0.69-2.38)	0.43		0.88 (0.72-1.08)	0.21
Fully-adjusted model*		1.11 (0.89-1.39)	0.36		0.93 (0.47-1.82)	0.83		0.82 (0.66-1.01)	0.06

†Depressive symptoms were defined as having a CES-D score ≥21.

* Adjusted for age, sex, living with a partner (yes, no), country of birth (France, other), educational level (≤ high school diploma, undergraduate degree, postgraduate degree), employment status (yes, no), BMI (<25, ≥25 and <30, ≥30) and personal history of CVD (yes, no).

Supplemental Table 2. Association between depressive symptoms and non-adherence to medications in volunteers with hypertension, diabetes and dyslipidaemia in the CONSTANCES cohort study, according to the duration of exposure to medications, 2012-2018 (odds ratios, ORs and 95% confidence intervals, CI).

	Hypertension			Diabetes			Dyslipidaemia		
	N cases/ N participants	OR (95% CI)	*P*	N cases/ N participants	OR (95% CI)	*P*	N cases/ N participants	OR (95% CI)	*P*
18 months	587/4,987			54/790			1,010/ 3,681		
Unadjusted model		1.32 (1.04-1.67)	0.02		1.85 (0.98-3.51)	0.06		1.17 (0.94-1.46)	0.15
Fully-adjusted model*		1.21 (0.94-1.55)	0.14		1.83 (0.91-3.70)	0.09		1.13 (0.90-1.43)	0.28
19-36 months	695/4,953			64/782			1,328/ 3,654		
Unadjusted model		1.28 (1.03-1.60)	0.03		1.44 (0.77-2.69)	0.25		0.91 (0.74-1.12)	0.37
Fully-adjusted model*		1.13 (0.90-1.43)	0.30		1.07 (0.54-2.11)	0.85		0.85 (0.68-1.07)	0.16

† Depressive symptoms were defined as having a CES-D score ≥22.

* Adjusted for age, sex, living with a partner (yes, no), country of birth (France, other), educational level (≤ high school diploma, undergraduate degree, postgraduate degree), employment status (yes, no), BMI (<25, ≥25 and <30, ≥30) and personal history of CVD (yes, no).

Supplemental Table 3. Association between depressive symptoms and non-adherence to medications in volunteers with hypertension, diabetes and dyslipidaemia in the CONSTANCES cohort study between the first 3-6 months, according to different thresholds of CES-D score, 2012-2018 (odds ratios, ORs and 95% confidence intervals, CI).

	Hypertension			Diabetes			Dyslipidaemia		
	N cases/ N participants	OR (95% CI)	*P*	N cases/ N participants	OR (95% CI)	*P*	N cases/ N participants	OR (95% CI)	*P*
CES-D score ≥19	700/4,996			48/793			963/3,691		
Unadjusted model		1.13 (0.92-1.38)	0.25		2.51 (1.37-4.60)	0.003		1.05 (0.87-1.29)	0.59
Fully-adjusted model*		1.10 (0.89-1.36)	0.37		2.44 (1.26-4.74)	0.009		1.06 (0.86-1.30)	0.60
CES-D score ≥21	700/4,996			48/793			963/3,691		
Unadjusted model		1.24 (1.00-1.53)	0.053		2.41 (1.28-4.52)	0.006		1.09 (0.88-1.35)	0.42
Fully-adjusted model*		1.21 (0.97-1.52)	0.09		2.40 (1.20-4.82)	0.01		1.10 (0.88-1.38)	0.38
CES-D score ≥22	700/4,996			48/793			963/3,691		

Unadjusted model	1.27 (1.02-1.59)	0.03	2.74 (1.46-5.15)	0.002	1.17 (0.94-1.46)	0.17
Fully-adjusted model*	1.24 (0.98-1.56)	0.07	2.80 (1.38-5.65)	0.004	1.19 (0.95-1.50)	0.14

* Adjusted for age, sex, living with a partner (yes, no), country of birth (France, other), educational level (≤ high school diploma, undergraduate degree, postgraduate degree), employment status (yes, no), BMI (<25, ≥25 and <30, ≥30) and personal history of CVD (yes, no).