DEDALE - Déterminants et évolution des états dépressifs : approche longitudinale en épidémiologie intégrative

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PRESENTATION DE LA CONSORTIUM

General background
Depression is one of the leading causes of disability worldwide. Besides cognitive, emotional and behavioral symptoms, depressed individuals display an increased risk of cardiovascular (CV) diseases (2) and poorer socio-economic outcomes. The mechanisms underlying these associations and their time frame remained poorly understood. Although CV diseases affect mainly older individuals, their association with depression may be explained by early biological processes, such as low-grade inflammation or metabolic consequences of a poor diet (5). In addition, although alcohol and substance use disorders are highly comorbid with depression and associated with its duration and outcomes, the interplay of depression and addictions remain relatively unexplored. Finally, although biomarkers are needed to refine our understanding of the pathophysiology and evolution of depressive states, promising tools such as neuroimaging have remained restricted to small, selected samples, thus yielding inconclusive results. The inclusion of a large, population-based sample is needed to conduct separate analyses across critical moderating factors such as age, gender or socio-economic status (SES). It will also provide sufficient statistical power to look for gene by environment (G x E) interactions that may predict depressive states over the lifespan.

Overall scientific approach and aims
The DEDALE research consortium will take advantage of data collected routinely in the CONSTANCES Cohort Study as well as of biological data (i.e. genetics, brain imaging and inflammation markers) that will be collected for a subsample. It will encompass 5 research projects (see below) linked by a general focus on risk factors and outcomes of depressive states in the general population. Each project will explore one specific aspect of these depressive states with both a cross-sectional and a longitudinal approach and will examine the following potential moderating factors: age, gender and SES. Given the rapid aging of the French population, specific attention will be paid to late-life depression.

Depressive states will be measured at baseline and every 3 years with the CESD scale. Variables collected at inclusion will include data on social and demographic characteristics, somatic health (with a focus on CV risk factors and diseases), health behaviors (with a focus on nutrition, tobacco, alcohol and cannabis consumption) and cognitive functions (with a focus on those altered by depression). Variables collected during the follow-up will include data on life events, material situation, employment (CNAV) and CV diseases (SNIIR-AM). Brain MRI data including resting state functional imaging will be collected for a subsample of 10,000 subjects. Additional biological data from the biobank will be used to provide measures of low-grade inflammation as well as genetic data regarding selected variants involved in vulnerability for depression or addiction. These genetic data will be extracted in a subsample of 20,000 participants whom parents were born in Europe and prioritizing those who underwent MRI scanning.
Project #1: Depression and genetic liability

The cross-sectional approach will describe how selected genetic variants are associated with current depressive states. The longitudinal approach will describe how G x E interactions might predict the incidence of new depressive states. As regards late-life depression, specific attention will be paid to the role of age-related life events such as retirement and bereavement.

Project #2: Depression and brain biomarkers

Brain imaging will not be performed at the same time than the assessment of depressive symptoms. The cross-sectional approach will thus describe brain correlates of “chronic or recurrent depressive states” defined as repeatedly having CESD scores above validated cut-off at three years of interval. Analyses will focus on two a priori biomarkers: hippocampal volume and resting state functional connectivity within the default mode and cognitive control brain networks. The longitudinal approach will confirm the ability of these biomarkers to predict future depressive states among participants free of history of depression at baseline.

In addition, outputs from project #1 will be used to compare brain biomarkers of depressive states with the neural correlates of genetic risk factors for depression among healthy subjects in a translational neuroscience perspective.

Project #3: Depression and addiction

The cross-sectional approach will describe the consumption of alcohol, tobacco and cannabis associated with depressive states in France according to gender, age and SES. The longitudinal approach will disentangle the causal relationship between depressive states and the consumption of alcohol, tobacco and cannabis.

In addition, outputs from projects #1 and #2 will be used to examine whether the comorbidity between depressive states and substance use disorders could be partially explained by common genetic or neural risk factors, respectively.

Project #4: Depression and cardiovascular diseases

The cross-sectional approach will describe to extent to which the association between depressive states and cardiovascular risk factors (including inflammation and poor diet) depends upon age, gender and SES. The longitudinal approach will describe the extent to which the association between depressive states and the incidence cardiovascular diseases depends upon age, gender and socio-economic status and will identify potential behavioral and biological explaining factors, focusing on nutrition and inflammation.

In addition, outputs from projects #1, #2 and #3 will be used to examine the potential confounding or mediating role of genetic risk factors of depression, brain functioning and substance use disorders, respectively.

Project #5: Depression and social outcome

The cross-sectional approach will describe social inequalities associated with depressive states, focusing on current occupational status, employment history, income and family situation and will identify factors potentially mediating or confounding these associations, focusing on cognitive functions. The longitudinal approach will try disentangling the respective role of social causation and social selection in the association of depressive states with the following outcomes: occupational status, employment history, family situation, sick leaves, occupational injuries and the mental component of the SF-12 scale. The longitudinal approach will also identify factors potentially mediating or confounding these associations, focusing on cognitive functions.
In addition, outputs from projects #1, #2, #3 and #4 will be used to examine the potential confounding or mediating role of genetic risk factors of depression, brain functioning, comorbid substance use disorders and poor CV health, respectively.

Project #5 will also produce a synthetic indicator of SES that will be used in other projects to examine the potential moderating role of SES.

**Added value of the consortium to the individual projects**

Each project will be in charge of the processing of specific data and will produce synthetic outputs that will be used not only 1) to achieve the main objectives of the project, but also 2) to inform the analyses of the other projects (see text above and Figure 1 below). Each project will thus take advantage of the expertise of the teams involved in the other projects. As described above, however, no project will fully depend upon the previous ones, so that any delay of one project will only minimally impact the other ones.

*Figure 1. Synergies within projects in the DEDALE research consortium.*

More generally, the multidisciplinary nature of the DEDALE research consortium is consistent with the urgent need for epidemiology, molecular biology and neurosciences to join forces in the search for the determinants of mental disorders (9). Finally, as shown by the number of shared Pubmed articles (see Figure 2 below), the teams of the DEDALE research consortium are already linked by past or ongoing scientific collaborations, paving the way for efficient and synergistic future collaborations within the present consortium.

Two plenary meetings will be held each year to ensure the monitoring of the DEDALE research consortium.

**Perspectives**

Expected results will help 1) refining our understanding of the etiology and pathophysiology of depressive states through the identification of genetic and environmental, potentially interacting, risk factors as well as reliable biomarkers, 2) describing the burden associated with comorbid substance use disorders and 3) defining at-risk groups and targets to inform interventions that would aim at preventing or reducing poor cardiovascular and social outcomes associated with depressive states. Perspectives beyond DEDALE include pharmaco-epidemiology studies based on the SNIIR-AM data to examine whether or not pharmacological treatment of depression and comorbid disorders are associated with improvement of these outcomes.
Figure 2. Number of shared PubMed articles between the DEDALE research consortium teams
**Background**

Major depression is one of the leading causes of disability worldwide. Several factors are involved in the etiology of major depression, including genetic and environmental factors, as well as their interplay through gene by environment (G x E) interactions. However, most of previous longitudinal studies were underpowered to look for additional moderation by age, gender or socio-economic status (SES). As regards age, previous G x E interaction studies addressing the risk of depressive disorders have mainly focused on adulthood and studies addressing late-life depression are rare. In the context of population aging, major depression in the elderly represents an increasing public health issue. Data are lacking regarding the interplay of age-related environmental risk factors, such as bereavement or retirement, with genetic vulnerability for depression.

**Objectives**

The present project will encompass both a cross-sectional and a longitudinal approach and examine the following potential moderating factors: age, gender and SES. Given the rapid aging of the French population, specific attention will be paid to late-life depression. The cross-sectional approach will describe how selected genetic variants are associated with current depressive states. The longitudinal approach will describe how G x E interactions might predict the incidence of new depressive states as well as the following outcomes: hospitalization for depression or suicidal attempt, suicide. As regards late-life depression, specific attention will be paid to the role of age-related life events such as retirement and bereavement.

**Methods**

Depressive states will be measured at baseline and every three years by the CESD scale. Genetic data will be extracted for a subsample of 20,000 participants whom parents were born in Europe. This subsample will be determined to optimize statistical power (i.e. oversampling those participants with depressive states, those reporting stressful life events on the first follow-up questionnaire, those with comorbid substance use disorders and those aged ≥60 years; see also project #3) and to include participants with brain MRI data (see also project #2). DNA extraction will be automatized. We already selected candidate SNPs based on the literature. Genotyping will be performed by using real-time PCR. The status of the Hardy-Weinberg equilibrium for the markers will be computed in the control subjects at least to avoid any error of the allele calling during the genotyping. We will format the data to fit with the database of the DEDALE Research Consortium and to transmit them to the other teams of the consortium. Analyses will be computed according to the genotypes for each variant to allow comparing additive effects and dominant models. We will also carry out haplotype analysis, which corresponds to the combined study of several SNPs encompassing the same gene and, in case of association, reinforces the discovery. Furthermore, we will compute epistatic effects which correspond to SNP x SNP interaction(s) studies.

**Perspectives**

Besides gaining knowledge about the genetic determinants of depressive states in the general population, the results of this project may eventually be used in personalized medicine as predictors of...
individual risk or clinical course. Perspectives include the use of the identified risk genetic markers in the other project of the DEDALE Research, looking for shared genetic liability with addiction (project #3) and cardiovascular diseases (project #4) for instance. Perspectives also include avenues of research in pharmacogenetics thanks to coupling with the SNIIRAM database.

**DEPRESSION AND BRAIN BIOMARKERS**

RESPONSABLE : Cédric Lemogne

**Background**

Major depression is one of the leading causes of disability worldwide. Although biomarkers are needed to refine our understanding of the pathophysiology and evolution of depressive states, promising tools such as neuroimaging have remained restricted to small, selected samples, thus yielding inconclusive results. At a brain level, functional MRI neuroimaging studies from our teams and others have found aberrant activation within the cortical midline structures to be associated with current depressive state, remitted depression and vulnerability for depression, including late-life depression, as well as with treatment response. As regards anatomical putative biomarkers, the smaller volume of hippocampus in depressed patients is a finding easy to replicate with standard methods but the multiplicity of factors moderating or mediating this “effect” makes it difficult to examine their role in samples of size typically encountered in neuroimaging research. The planned sample size for CONSTANCES subjects who will beneficiate from a MRI scan (i.e. 10,000), as well as the possibility of coupling these anatomical data with biographical and genetic data make CONSTANCES the ideal platform to address these questions.

**Objectives**

A cross-sectional approach will describe the brain correlates of “chronic or recurrent depressive states”. Analyses will focus on two a priori biomarkers: hippocampal volume and resting state functional connectivity within the default mode network and the cognitive control network. A longitudinal approach will confirm the ability of these biomarkers to predict future depressive states among participants free of history of depression at baseline. In addition, outputs from project #1 will be used to compare brain biomarkers of depressive states with the neural correlates of genetic risk factors for depression among healthy subjects in a translational neuroscience perspective. Finally, the present project will produce synthetic inputs in order to inform the other projects of the DEDALE Research Consortium as brain functioning may explain the association of depressive states with some specific features including substance use (project #3), cardiovascular diseases and elevated inflammation (project #4) or cognitive impairment (project #5).

**Methods**

The cross-sectional approach will compare participants with “chronic or recurrent depressive states”, defined as repeatedly having CESD scores above validated cut-off at three years of interval, to age, gender and SES-matched control subjects with a 2:1 ratio. The longitudinal approach will compare participants with and without a depressive state at follow-up among those free of history and symptoms of depression at baseline. Hippocampal volume will be calculated based on a combination of voxel-based morphometry (VBM) with normalization by the DARTEL algorithm. As regards functional connectivity at rest, two approaches will be used. An a priori seed-based approach will be used to identify the cognitive control network and the default mode network. Further exploratory analyses will use a methodology derived from Independent Component Analysis (i.e. Multi-Scale Individual Component Clustering).
Perspectives
The expected results will contribute to identify clinically relevant biomarkers of depressive states that could eventually be used in the personalized management of depressive states. Perspectives beyond the current project include the identification of brain predictors of response to antidepressant drugs thanks to a coupling with the SNRIRAM data.

DEPRESSION AND ADDICTION

RESPONSABLE: Frédéric Limosin

Background
Major depression is one of the leading causes of disability worldwide and often co-occurs with substance use disorders. This comorbidity is associated with poorer outcomes for both conditions but potential mechanisms are not fully understood and may vary by type of substance used and differ in effects across subgroups of the population (e.g., sex, age and SES). Data are especially lacking for cannabis and, whatever the substance, for older adults. Like the other projects of the DEDALE research consortium, the present project will encompass both a cross-sectional and a longitudinal approach. Given the rapid aging of the French population, specific attention will also be paid to late-life depression.

Objectives
The specific aims of this project are:

1. To describe the prevalence of consumption of alcohol, tobacco and cannabis associated with depressive states in France according to gender, age and SES.

2. To examine simultaneously whether sex, age and SES disparities in the prevalence or effects of alcohol, tobacco and cannabis consumption contribute respectively to sex, age and SES differences in the prevalence of depressive states.

3. To determine the specificity of effects of each drug on depressive states.

4. To disentangle the causal relationships between consumption of alcohol, tobacco and cannabis and depressive states.

Methods
Depressive states will be measured at baseline and every three years by the CESD scale. General Linear Model (GLM) will be used to examine sex, age and SES differences in the prevalence of each substance and the conditional risk of depression by substance. Structural equation model (SEM) with moderated mediation will be used to test the presence of moderating effects while simultaneously taking into account age differences in the prevalence of substance types. Since substance use disorders often co-occur, we will combine confirmatory factor analysis (CFA) or exploratory factor analysis with SEM to determine the extent to which the association between substance use and depressive states is specific to each substance and the extent to which it is due to co-occurring use of more than one substance. The hypothesis that the predominant direction of the bidirectional association is from substance use to depressive states will be tested with both instrumental variable and propensity score methods.

Perspectives
Examining the reasons for the strong association between major depression and each substance use disorder would advance our understanding of the etiology of these disorders and help develop more effective treatment and preventive interventions. Examining whether this comorbidity is more frequent / more detrimental in particular subgroup(s) of the population and understanding the reasons for this hypothesized heightened vulnerability in specific subgroups would be crucial to implement personalized interventions.

**DEPRESSION AND CARDIOVASCULAR DISEASES**

**RESPONSABLE : Hermann Nabi**

**Background**

Major depression is one of the leading causes of disability worldwide and is associated with an increased risk of cardiovascular (CV) mortality. The underlying mechanisms of this association remained poorly understood. Positive studies may have overlooked some potential confounding or mediating factors, such as hazardous health behaviors (e.g. at-risk dietary patterns, smoking, alcohol misuse, or poor medical treatment adherence), poor social support, reduced quality of care and inflammation. On the other hand, negative studies may have overlooked the role of moderating factors such as gender or socio-economic status (SES).

**Objectives**

A cross-sectional approach will examine the moderating effect of age, gender and SES in the association between depressive symptoms and CV risk factors (i.e. dyslipidemia, obesity, at-risk diet, tobacco and alcohol consumption, lack of physical activity, diabetes and hypertension), including resting heart rate and inflammation. A longitudinal approach will examine: 1) the moderating effect of age, gender and SES in the association between depressive symptoms and several CV outcomes: incident hypertension, coronary heart disease and stroke, deaths from coronary heart disease or stroke, global cardiovascular mortality; 2) the mediating role of selected behavioral and biological factors in these associations: at-risk diet, resting heart rate, C-reactive protein, interleukin-6, tumor necrosis factor-alpha and neutrophil/lymphocyte ratio. In addition, outputs from the other projects of the DEDALE Research Consortium will be used to examine the potential confounding or mediating role of genetic risk factors of depression (project #1), brain functioning (project #2) and substance use disorders (project #3), respectively.

**Methods**

Depressive states will be measured at baseline and every three years by the CESD scale. CV risk factors will be collected through questionnaire and biometric and biological data. Based on a qualitative food frequency questionnaire, a principal component analysis (PCA) will identify dietary patterns at baseline. Regarding inflammation, the following measures will be collected: C-reactive protein, interleukin-6, tumor necrosis factor-alpha, neutrophil/lymphocyte ratio. Incident coronary heart disease and stroke will be carefully validated by an external committee.Deaths from coronary heart disease or stroke and global cardiovascular mortality will be collected from the CépiDC. Incident hypertension will be inferred from questionnaires and SNIRAM data. Associations between depressive symptoms and CV risk factors will be examined among all included participants with general linear model or binary logistic regression for continuous or binary variables. Associations between depressive symptoms and CV outcomes will be examined among participants aged 35 or more with cox regressions. Should a significant interaction be
found between depressive symptoms and age, gender or SES as regards a specific CV risk factor or outcome, post hoc subgroup analyses will be performed to describe this interaction in details. The hypothesis of a potential confounding or mediating role of any factor will tested with a bootstrap-based “causal” mediation analysis.

**Perspectives**

A better understanding of the potential mediating, confounding or moderating factors of the association between depressive symptoms and cardiovascular diseases is warranted to inform targeted preventive interventions.

**DEPRESSION AND SOCIAL OUTCOME**

**RESPONSABLE:** Maria Melchior

**Background**

Research has observed large social inequalities with regard to depression, whereby individuals with low socioeconomic position are more likely to be depressed and have severe and persistent symptoms. However the contribution of socioeconomic position to depression and the impact of depressive symptoms on socioeconomic position are not yet fully understood. One aspect that is not yet elucidated is the role of different socioeconomic characteristics over the short and long-term. Another area that requires investigation is the contribution of access to treatment to socioeconomic inequalities in depression. Finally, the impact of depression may be different depending on individuals’ socioeconomic position, but data on this topic are rare.

**Objectives**

The aims of this project will be to test long-term associations between socioeconomic characteristics such as educational attainment, occupational grade, employment status, financial resources and migrant status and depression as well as access to treatment in case of depressive symptoms. Moreover, among individuals depressed at study baseline, we will study changes in socioeconomic position from baseline onwards. Data from the CONSTANCES cohort study is particularly suitable for this project for several reasons: a) large sample size; b) validated measures of depressive symptoms; c) multiple measures of socioeconomic position including occupational trajectories; d) access to data on antidepressant treatment and hospitalizations due to depression.

**Methods**

Depressive states will be measured at baseline and every three years by the CESD scale. Data will be analyzed controlling for factors such as sex, age, marital status, life events, health behaviors and overweight and using the most appropriate statistical methods (logistic and linear regression for cross-sectional data, Cox regression or GEE models for prospective analyses depending on whether they are based on repeated measures or not). We will systematically test for age and sex differences in associations between socioeconomic position and depression.

**Perspectives**

The results of this study will help understand the mechanisms underlying socioeconomic inequalities in depression, and potentially inform strategies aiming to decrease them.