Depression, Cognitive Functions, and Impaired Functioning in Middle-Aged Adults From the CONSTANCES Cohort

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ABSTRACT

Objective: This large-scale population-based prospective study examined the association between depressive symptoms and cognitive performance at baseline with later functioning in middle-aged adults.

Methods: The Center for Epidemiologic Studies Depression Scale, the Digit Symbol Substitution Test (DSST), the Trail Making Test B (TMT-B), and the Semantic Verbal Fluency test (SVF) were completed at baseline by 7,426 participants aged ≥ 45 years from February 2012 to December 2013. Role limitations and social functioning were later assessed with the second version of the 12-Item Short Form Health Survey. The association between depressive symptoms and cognitive performance at baseline with functioning at follow-up was examined using general linear models and mediation analyses including sex, age, education, alcohol intake, and cannabis use as covariates.

Results: Altered functioning at follow-up was predicted by depressive symptoms (β per standard deviation [95% confidence intervals]: −1.10 [−1.16 to −1.03] and −1.02 [−1.08, −0.96] for role limitations and social functioning, respectively) and DSST, TMT-B, and SVF performance (for role limitations: 0.11 [0.09 to 0.14], −0.11 [−0.13 to −0.08], and 0.03 [0.01 to 0.06], respectively; for social functioning: 0.10 [0.07 to 0.12], −0.08 [−0.11 to −0.06], and 0.04 [0.01 to 0.05], respectively) at baseline. Depressive symptoms were associated with poorer cognitive performance at baseline (−0.19 [−0.25 to −0.13], 0.15 [0.08 to 0.21], and −0.11 [−0.17 to −0.04], respectively). Cognitive performance accounted for only 0.3%–1.4% of the relationship between depressive symptoms and functioning. In contrast, depressive symptoms accounted for 19.5%–43.7% of the association between cognitive performance and functioning.

Conclusions: In middle-aged adults from the general population, cognitive impairment is unlikely to substantially explain the association between depressive symptoms and later role limitations and social functioning.

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Depression affects 350 million people worldwide and is a major contributor to the overall global burden of disease.[1] Depression is strongly associated with functional impairment,[2] which has been found to be comparable to or worse than that associated with several major chronic medical conditions (eg, diabetes, arthritis, angina).[3] Impaired subjective performance has been reported in widespread domains of functioning, such as household; work; relationships with partners, family members, and friends; and leisure activities.[4,5] These impairments in functioning are strongly associated with the severity of depressive symptoms[6,7] and reduced quality of life.[8] In addition, depression may contribute to objective social damage, such as work absenteeism, presenteeism, and unemployment.[7,9] Several studies have reported a significant positive effect of antidepressant treatments on quality of life and on social and work functioning,[10] although residual functional impairment is frequent in patients who achieved remission.[11] However, the mechanisms underlying the association between depression and functioning remain largely unknown. In recent decades, it has been suggested that cognitive dysfunctions associated with depression might mediate its impact on functioning.[12,13] Indeed, a broad range of cognitive domains may be affected in depressed patients, such as information processing speed, verbal fluency, working memory, attentional control, and cognitive inhibition.[14,15] Such cognitive impairments, which all relate to some extent to executive function, have even been found in patients during their first depressive episode.[16,17] While cognitive function may improve after pharmacologic treatment of depression,[18,19] deficits can still be detected in euthymic patients,[20,21] which might explain persistent functional impairment in remission.

Several studies have reported an association between objectively assessed cognitive dysfunction and functional impairment in patients with depression.[12,13] For example, Jaeger et al[22] reported that several cognitive measures were associated with disability 6 months following

Clinical Points

- Depression is associated with both cognitive and functional impairment.
- In middle-aged adults from the general population with depressive symptoms, cognitive impairment is unlikely to substantially explain altered functioning.
- Interventions aimed at reducing the functional impairment associated with depression should primarily target depressive symptoms themselves; such interventions are likely to improve cognitive functioning at the same time.

hospitalization for a major depressive episode in 48 patients; in addition, 6-month cognitive performance was strongly associated with self-reported functioning after adjusting for residual depression. In 21 adults treated for depression, Naismith et al[23] found a moderate relationship between objectively measured psychomotor speed and physical disability, even after adjusting for depression severity. In 52 inpatients with depression, Withall et al[24] found that poor event-based prospective memory and more perseverative errors on the shortened Wisconsin Card Sorting Test at admission predicted worse social and occupational outcomes at a 3-month follow-up. Considering occupational status, Baune et al[25] reported that, among 70 patients with depression, those who were unemployed had poorer results on neuropsychological tests than those who were employed. Finally, in 483 currently non-depressed patients with major depressive disorder receiving selective serotonin reuptake inhibitors, improvements in cognitive performance were found to predict improvements in functioning.[26]

Overall, these studies are consistent with the hypothesis that cognitive impairment may account for a substantial part of functional limitation in patients with depression. However, in contrast with more severe mental disorders such as schizophrenia or bipolar disorder,[27] the evidence supporting this hypothesis remains weak. Most of the aforementioned studies were based on relatively small, highly selected samples; few had a longitudinal design; and none performed formal mediation analyses.[12,28,29] In a cross-sectional survey including 21,425 adults from 6 European countries, Buist-Bouwman et al[30] reported that more than 25% of the association of depression with role functioning was directly attributable to self-reported cognitive complaints (ie, concentration, attention, and memory problems). However, that large-scale study did not use objective measures of cognitive function or have a longitudinal design. Besides, due to its associations with both impaired cognition and altered functioning, depression is a plausible confounding factor that may partly explain the association between cognitive and functional impairment.

In this study, we used data from CONSTANCES, a French large-scale population-based study, to investigate the prospective associations between depressive symptoms and cognitive functions with later functioning in middle-aged adults.

METHODS

Participants

All participants were recruited from the CONSTANCES cohort (www.constances.fr). This project aims at providing a general prospective cohort of a large sample of the French population aged 18–69 years.[31,32] Participants were recruited since 2012 among people affiliated to the main national health insurance provider, which covers more than 85% of the French population. The cohort was designed to be representative of the target population according to age, sex, employment status, and occupational class. A random sample from the target population was invited by mail to join the cohort. Those who agreed had to fill out self-administrated questionnaires dealing with lifestyle, health, physical limitations, and social and personal characteristics. They were invited to go to one of the 21 participating Health Screening Centers throughout France to benefit from an extensive health examination (medical and paraclinical examinations, blood tests). In addition, cognitive tests were performed for those aged 45 years or older. A follow-up self-administered questionnaire was then completed annually by the participants at home, using either paper or web-based questionnaires.

In the present study, we used data from the participants aged 45 years or older included from February 21, 2012, to December 31, 2013. Eligibility criteria were being able to fill out the study questionnaires, ability to speak French, and having no missing data for selected variables, including assessment of functioning at follow-up in 2014 (Supplementary Figure 1).

All confidentiality, safety, and security procedures were approved by the French legal authorities. In accordance with French regulations, the CONSTANCES cohort project obtained the authorization of the National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés). Written informed consent was obtained from all participants.

Assessment of Depressive Symptoms at Baseline

Depressive symptoms were measured at baseline with the French version of the Center for Epidemiologic Studies Depression Scale (CES-D).[33,34] The total score ranged from 0 (no depressive symptom) to 60. We used a cutoff score of 19 (CES-D score ≥ 19 versus < 19) to define depression status[34] (Appendix 1).

Assessment of Cognitive Functions at Baseline

Cognitive functions were assessed at baseline using objective neuropsychological tests for which impaired performance has been previously reported in patients with major depression[15]: Digit Symbol Substitution Test (DSST),[35] Trail Making Test part B (TMT-B),[36] and Semantic Verbal Fluency test (SVF)[37] (Appendix 1). TMT-B score was log transformed to achieve a close-to-normal distribution. All of these tests engage executive function to some extent.

Assessment of Functioning at Follow-Up

The second version of the Short-Form-12 Health Survey (SF-12v2)[38–40] was part of the annual follow-up questionnaire sent in 2014 to all participants (Appendix 1). Mean (SD) duration between baseline assessments and reception of the 2014 follow-up questionnaire was 497 (157) days. Because we were interested in functional impairment associated with depression specifically, we decided a priori to use 2 subscales as primary outcomes, as Spijker et al[41] did: role limitations due to emotional problems, henceforth referred to as "role limitations" (score range, 2–10), and social functioning (score range, 1–5). For both scales, a higher score corresponds with better functioning.

Other Covariates

Other covariates included age at baseline, sex, year of inclusion, education level (no diploma, lower secondary education, professional education, upper secondary education, bachelor, fourth-year university level, master's degree or higher, other), alcohol intake frequency (never, once or less than once in a month, 2 or 3 times in a month, once or more in a week), and lifetime cannabis use. Education level, alcohol intake frequency, and lifetime cannabis use were assessed at baseline.

Statistical Analysis

Cognitive and functioning scores were *z*-transformed. The relationships between variables were assessed within the framework of generalized linear models (GLMs) using R software (http://cran.r-project.org, version 3.3.1). First, analyses were conducted including role limitations and social functioning at follow-up as the dependent variables and depression status at baseline as the independent variable. Sex, age, year of inclusion, education level, alcohol intake frequency, and lifetime cannabis use at baseline were entered as covariates. The association between depression status (as a binary variable) and each cognitive score at baseline was also assessed. Then, each of the 3 cognitive scores (DSST, TMT-B, SVF) was entered as the independent variable instead of depression status in 3 separate models. Finally, both depression status and cognitive scores were entered in the 3 separate models. GLM coefficients were presented per standard deviation of the SF-12v2 subscale.

To examine whether changes in regression coefficients across the aforementioned models were statistically significant, formal mediation analyses were conducted with functioning scores as the dependent variable based on algorithms devised by Imai et al.[42] Sex, age, year of inclusion, education level, alcohol intake frequency, and lifetime cannabis use at baseline were entered as covariates.

Table 1. Associations of Depression Status and Cognitive Performance at Baseline With Role Limitations and Social Functioning at Follow-Up in Multivariate Models (N = 7,426)[a]

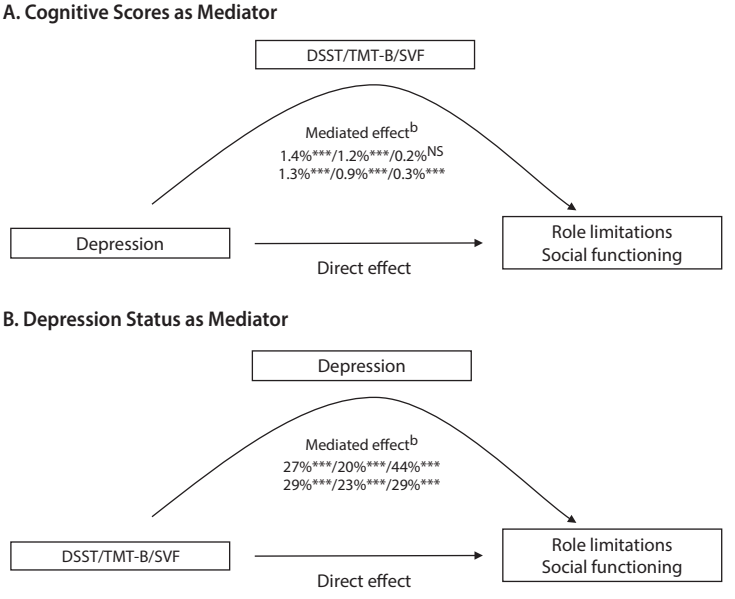
	Depression Status[b]				DSST				TMT-B				SVF			
Model	β[c]	CI[d]	%Med[e]	%CI[f]	β[c]	CI[d]	%Med[g]	%CI[f]	β[c]	CI[d]	%Med[g]	%CI[f]	β[c]	CI[d]	%Med[g]	%CI[f]
Model Using Role Limitations as the Dependent Variable																
1	−1.10	−1.16 to −1.03	Ref	Ref												
2a					0.11	0.09 to 0.14	Ref	Ref								
2b									−0.11	−0.13 to −0.08	Ref	Ref				
2c													0.03	0.01 to 0.06	Ref	Ref
3a	−1.08	−1.14 to −1.02	1.44	0.93 to 2.21	0.08	0.06 to 1.05	26.77	19.47 to 36.93								
3b	−1.08	−1.14 to −1.02	1.19	0.64 to 1.82					−0.09	−0.11 to −0.06	19.53	11.17 to 28.33				
3c	−1.09	−1.15 to −1.03	0.15[NS]	−0.03 to 0.49									0.02[NS]	−0.01 to 0.04	43.72	18.34 to 118.97
Model Using Social Functioning as the Dependent Variable																
1	−1.02	−1.08 to −0.96	Ref	Ref												
2a					0.10	0.07 to 0.12	Ref	Ref								
2b									−0.08	−0.11 to −0.06	Ref	Ref				
2c													0.04	0.01 to 0.05	Ref	Ref
3a	−1.01	−1.07 to −0.94	1.31	0.85 to 1.97	0.07	0.04 to 0.09	29.11	20.19 to 40.17								
3b	−1.01	−1.07 to −0.95	0.92	0.49 to 1.46					−0.06	−0.09 to −0.04	23.45	14.11 to 35.09				
3c	−1.02	−1.08 to −0.95	0.33	0.07 to 0.71									0.03	0.01 to 0.05	29.39	12.09 to 58.12

[a]All statistics were significant ($P < .001$), except when noted. Independent variables are as follows: depression status in Model 1, DSST in Model 2a, TMT-B in Model 2b, and SVF in Model 2c. Models 3a, 3b, and 3c include depression status as the independent variable and were adjusted for DSST (Model 3a), TMT-B (Model 3b), and SVF (Model 3c). All models were also adjusted for sex, age, year of inclusion, education level, alcohol intake frequency, and lifetime cannabis use.
[b]Center for Epidemiologic Studies Depression Scale (CES-D) score ≥ 19.
[c]β = estimated parameter (GLM coefficient) per standard deviation of the subscale of the second version of the 12-item Short Form Health Survey (SF-12v2).
[d]CI = 95% confidence interval of the estimated parameter.
[e]%Med = proportion of total effect via mediation in mediation analyses using cognitive scores as mediator.
[f]%CI = 95% confidence interval of the mediation proportion.
[g]%Med = proportion of total effect via mediation in mediation analyses using depression status as mediator.
Abbreviations: DSST = Digit Symbol Substitution Test (total score), NS = not significant, Ref = reference value, SVF = Semantic Verbal Fluency test (total score), TMT-B = Trail Making Test B (total time, log-transformed).

First, depression status at baseline was considered as the independent variable, and cognitive scores at baseline (DSST, TMT-B, and SVF separately) as the "mediator" variables between depression status at baseline and functioning at follow-up. Then, each cognitive score was entered as the independent variable with depression status at baseline as the "mediator" variable between each cognitive score at baseline and functioning at follow-up. These mediation models were fit with GLM, and output objects were bootstrapped 500 times with replacement using a parametric mediational analysis. In mediation analysis, a significant mediating effect is defined by a 95% confidence interval (CI) of the regression coefficient that does not include zero.[42]

To examine the robustness of our findings, we also carried out sensitivity analyses. We performed similar analyses (1) using CES-D as a continuous score, taking the interval between the 25th and the 75th percentile as the unit to provide clinically meaningful regression coefficients; and (2) using a more restricted definition for depression requiring both CES-D score ≥ 19 and self-reported limitation at inclusion. Self-reported limitation at inclusion was defined as having answered "yes" to "Have you been limited, for at least 6 months, in your routine activities by a health problem?" and then having answered "depressive state" to "If yes, for what reasons?"

Figure 1. Graphic Representation of Mediation Analyses[a]



[a]Cognitive scores served as a mediator of the relationship between depression status and role limitations/social functioning at follow-up (A). Depression status served as a mediator of the relationship between cognitive scores and role limitations/social functioning at follow-up (B). Covariates are sex, age, year of inclusion, education level, alcohol intake frequency, and lifetime cannabis use.

[b]Proportions of mediated effect are listed as follows: top row: models using DSST/TMT-B/SVF total scores, with role limitations as dependent variable; bottom row: models using DSST/TMT-B/SVF total scores, with social functioning as dependent variable.

***$P < .001$.

Abbreviations: DSST = Digit Symbol Substitution Test (total score), NS = not significant ($P > .05$), SVF = Semantic Verbal Fluency (total score), TMT-B = Trail Making Test B (total time).

RESULTS

The final study population consisted of 7,426 participants (3,551 men, 47.82%) with a mean (SD) age of 57.79 (7.20) years. Study population selection is described in Supplementary Figure 1. The mean (SD) CES-D score was 9.88 (8.35) (range, 0–53); 13.24% of participants (n = 983) were depressed at baseline (CES-D score ≥ 19) (Supplementary Table 1). Characteristics of participants lost to follow-up and comparisons with the study population are displayed in Supplementary Table 2.

First, after adjustment for covariates, depression status was significantly associated with each of the 3 cognitive scores at baseline as expected (DSST: β = −0.19; 95% CI, −0.25 to −0.13; $P < .001$; TMT-B: β = 0.15; 95% CI, 0.08 to 0.21; $P < .001$; SVF: β = −0.11; 95% CI, −0.17 to −0.04; $P = .001$) and with both functioning scores (role limitations and social functioning) at follow-up (Table 1). Second, each of the 3 cognitive scores at baseline was significantly associated with the 2 functioning scores at follow-up as expected (Table 1). Third, after further adjustment for each cognitive score, the relationship between depression status and functioning remained virtually unchanged, and mediation analyses showed that cognitive scores at baseline accounted for only 0.3%–1.4% of the relationship between depression status at baseline and functioning at follow-up (Table 1, Figure 1). In contrast, depression status at baseline accounted for 19.5%–43.7% of the relationship between cognitive at baseline and functioning scores at follow-up (Table 1, Figure 1).

In sensitivity analyses based on continuous CES-D scores, depressive symptoms were also associated with each of the 3 cognitive scores (DSST: β = −0.10; 95% CI, −0.12 to −0.07; $P < .001$; TMT-B: β = .09; 95% CI, 0.07 to 0.12; $P < .001$; SVF: β = −0.06; 95% CI, −0.08 to −0.03; $P < .001$) and with both functioning scores (Table 2). The association between depressive symptoms and the 2 functioning scores remained virtually unchanged after further adjustment for each cognitive score, which accounted for only 0.2%–1.1% of this relationship ($P < .001$ considering DSST and TMT-B, not significant for SVF) (Table 2). In contrast, continuous CES-D scores accounted for 42.5%–85.3% of the relationship between cognitive and functioning scores (all $P < .001$) (Table 2).

When a more restricted definition of depression status is used, combining both CES-D score ≥ 19 and self-reported limitation (n = 205, ie, 2.76% of the total sample), the association of depression status with each of the cognitive scores (DSST: β = −0.34; 95% CI, −0.47 to −0.22; $P < .001$; TMT-B: β = .29; 95% CI, 0.16 to 0.42; $P < .001$; SVF: β = −0.25; 95% CI, −0.38 to −0.11; $P < .001$) and with both functioning scores (Table 3) strengthened. However, cognitive scores accounted for only

0.6%–2.1% of the relationship between CES-D scores and functioning, whereas depression status still explained 13.3%–33.8% of the relationship between cognitive and functioning scores (all $P < .001$) (Table 3).

DISCUSSION

This prospective large-scale population-based study aimed to investigate the association of depressive symptoms and cognitive performance at baseline with both role limitations and social functioning at follow-up in adults aged 45 years or older. We found that the association between depressive symptoms and later functioning was not substantially explained by cognitive performance, regardless of the definition of depression (ie, binary or continuous), the cognitive test (ie, DSST, TMT-B or SVF), or the functioning variable (ie, role limitations or social functioning). In contrast, depression explained a substantial proportion of the association between cognition at baseline and functioning at follow-up.

Strengths of the study are the large size, the population-based sample, the prospective design, and the use of objective measures of cognitive functions. Thanks to a sufficient statistical power and standardized neuropsychological tests, our results were consistent with decades of literature linking depressive symptoms with both cognitive[14,15] and functional[2–6,8–11] impairment. However, it is noteworthy that this literature did not examine the contribution of cognitive function or functional impairment associated with depression. To our knowledge, our study might indeed be the first to explore this issue in a large prospective sample.

Some limitations should also be acknowledged. First, the population study is not representative of the general population and was confined to participants aged 45 to 69 years. Thus, our results cannot be generalized to younger or older adults. Second, the duration of the follow-up was short. However, the majority of the studies on this topic have been cross-sectional. Third, the diagnosis of depression was based on a self-report scale rather than on a standardized interview. However, sensitivity analyses using CES-D as a continuous score or a more restricted definition of depression status (including both CES-D score ≥ 19 and self-reported limitation at baseline) yielded similar results. Fourth, as in other studies on this topic,[40] functioning was measured with a self-administered questionnaire (ie, the SF-12v2).

Table 2. Associations of Depressive Symptoms (CES-D Score) and Cognitive Performance at Baseline With Role Limitations and Social Functioning at Follow-Up in Multivariate Models (N = 7,426)[a]

	Depressive Symptoms (CES-D Score)[b]				DSST				TMT-B				SVF			
Model	β[c]	CI[d]	%Med[e]	%CI[f]	β[c]	CI[d]	%Med[g]	%CI[f]	β[c]	CI[d]	%Med[g]	%CI[f]	β[c]	CI[d]	%Med[g]	%CI[f]
Model Using Role Limitations as the Dependent Variable																
1	−0.56	−0.59 to −0.54	Ref	Ref												
2a					0.11	0.09 to 0.14	Ref	Ref								
2b									−0.11	−0.13 to −0.08	Ref	Ref				
2c													0.03	0.01 to 0.05	Ref	Ref
3a	−0.56	−0.58 to −0.53	1.08	0.67 to 1.58	0.06	0.04 to 0.08	45.53	35.80 to 57.00								
3b	−0.56	−0.58 to −0.53	1.03	0.66 to 1.52					−0.06	−0.08 to −0.04	42.51	33.01 to 54.26				
3c	−0.56	−0.59 to −0.54	0.06[NS]	−0.14 to 0.27									0.00[NS]	−0.01 to 0.03	85.28	50.00 to 566.79
Model Using Social Functioning as the Dependent Variable																
1	−0.53	−0.56 to −0.51	Ref	Ref												
2a					0.10	0.07 to 0.12	Ref	Ref								
2b									−0.08	−0.11 to −0.06	Ref	Ref				
2c													0.04	0.02 to 0.06	Ref	Ref
3a	−0.53	−0.55 to −0.50	0.88	0.51 to 1.42	0.05	0.03 to 0.07	49.05	36.38 to 65.42								
3b	−0.53	−0.55 to −0.51	0.72	0.34 to 1.16					−0.04	−0.06 to −0.02	53.95	38.32 to 91.36				
3c	−0.53	−0.56 to −0.51	0.21	0.03 to 0.49									0.02	0.00 to 0.04	55.69	36.78 to 109.99

[a]All statistics were significant ($P < .001$), except when noted. Independent variables are as follows: depression status in Model 1, DSST in Model 2a, TMT-B in Model 2b, and SVF in Model 2c. Models 3a, 3b, and 3c include depression status as the independent variable and were adjusted for DSST (Model 3a), TMT-B (Model 3b), and SVF (Model 3c). All models were also adjusted for sex, age, year of inclusion, education level, alcohol intake frequency, and lifetime cannabis use.
[b]Center for Epidemiologic Studies Depression Scale (CES-D) score, taking the interval between the 25th and the 75th percentile (9.56) as unit.
[c]β = estimated parameter (GLM coefficient) per standard deviation of the subscale of the second version of the 12-item Short Form Health Survey (SF-12v2).
[d]CI = 95% confidence interval of the estimated parameter.
[e]%Med = proportion of total effect via mediation in mediation analyses using cognitive scores as mediator.
[f]%CI = 95% confidence interval of the mediation proportion.
[g]%Med = proportion of total effect via mediation in mediation analyses using depression status as mediator.
Abbreviations: DSST = Digit Symbol Substitution Test (total score), NS = not significant, Ref = reference value, SVF = Semantic Verbal Fluency test (total score), TMT-B = Trail Making Test B (total time, log-transformed).

Table 3. Associations of Restricted Depression Status and Cognitive Performance at Baseline With Role Limitations/Social Functioning at Follow-Up in Multivariate Models (N = 7,426)[a]

	Restricted Depression Status[b]				DSST				TMT-B				SVF			
Model	β[c]	CI[d]	%Med[e]	%CI[f]	β[c]	CI[d]	%Med[g]	%CI[f]	β[c]	CI[d]	%Med[g]	%CI[f]	β[c]	CI[d]	%Med[g]	%CI[f]
Model Using Role Limitations as the Dependent Variable																
1	−1.56	−1.69 to −1.43	Ref	Ref												
2a					0.11	0.09 to 0.14	Ref	Ref								
2b									−0.11	−0.13 to −0.08	Ref	Ref				
2c													0.03	0.01 to 0.05	Ref	Ref
3a	−1.53	−1.66 to −1.40	2.07	1.24 to 3.04	0.09	0.07 to 0.12	16.69	10.92 to 23.21								
3b	−1.53	−1.66 to −1.40	1.78	1.00 to 2.82					−0.09	−0.12 to −0.07	13.32	7.63 to 19.84				
3c	−1.55	−1.69 to −1.42	0.31[NS]	−0.02 to 0.75									0.02[NS]	−0.01 to 0.04	33.76	16.70 to 122.62
Model Using Social Functioning as the Dependent Variable																
1	−1.38	−1.51 to −1.24	Ref	Ref												
2a					0.10	0.07 to 0.12	Ref	Ref								
2b									−0.08	−0.11 to −0.06	Ref	Ref				
2c													0.04	0.02 to 0.07	Ref	Ref
3a	−1.35	−1.48 to −1.22	1.99	1.22 to 3.08	0.08	0.06 to 0.11	16.89	11.05 to 23.39								
3b	−1.36	−1.49 to −1.22	1.43	0.74 to 2.36					−0.07	−0.09 to −0.05	15.07	9.16 to 22.47				
3c	−1.37	−1.50 to −1.24	0.61	0.20 to 1.22									0.04	0.01 to 0.06	21.38	10.63 to 48.39

[a]All statistics were significant ($P < .001$), except when noted. Independent variables are as follows: depression status in Model 1, DSST in Model 2a, TMT-B in Model 2b, and SVF in Model 2c. Models 3a, 3b, and 3c include depression status as the independent variable and were adjusted for DSST (Model 3a), TMT-B (Model 3b), and SVF (Model 3c). All models were also adjusted for sex, age, year of inclusion, education level, alcohol intake frequency, and lifetime cannabis use.
[b]Center for Epidemiologic Studies Depression Scale (CES-D) score ≥ 19 and self-reported limitation.
[c]β = estimated parameter (GLM coefficient) per standard deviation of the subscale of the second version of the 12-item Short Form Health Survey (SF-12v2).
[d]CI = 95% confidence interval of the estimated parameter.
[e]%Med = proportion of total effect via mediation in mediation analyses using cognitive scores as mediator.
[f]%CI = 95% confidence interval of the mediation proportion.
[g]%Med = proportion of total effect via mediation in mediation analyses using depression status as mediator.
Abbreviations: DSST = Digit Symbol Substitution Test (total score), NS = not significant, Ref = reference value, SVF = Semantic Verbal Fluency test (total score), TMT-B = Trail Making Test B (total time, log-transformed).

In particular, one may argue that the items that were selected a priori from the SF-12v2 are intrinsically connected to depressive symptoms so that there might be little room for a mediating effect of objective cognitive functioning. However, it should be noted that not only depressive symptoms but also cognitive functions were associated with the 2 SF-12v2 subscales, suggesting that these measures were sensitive enough to capture relevant effects. Furthermore, depressive symptoms did account for a substantial part of the association between cognitive functions and these 2 subscales. Therefore, the lack of mediation effect by cognitive functions is unlikely to be explained by the subjective versus objective nature of the measures. Finally, our analyses did not control for intelligence quotient (IQ). Future studies would benefit in reproducing our results while additionally adjusting for IQ, particularly for cognitive tests that are closely related to IQ. For example, in older adults, TMT score has been found to be more strongly associated with IQ than education level.[43] However, IQ may also be considered as the composite of neurobehavioral abilities assessed in neurocognitive tests.[44] In this study, analyses were adjusted for education level, which has been found to be positively associated with both IQ and neuropsychological test performance.[45] For example, a recent study[46] reported a positive association between education level and cognitive scores, especially on more cognitively complex tests such as the TMT-B or the DSST, in contrast with more simple tests such as the TMT-A. Thus, schooling may foster the development of cognitive processes that underpin performance on IQ.

This study confirms results from previous ones[2–6,8–11] of a strong association between depression and later altered functioning. We found that both social functioning and role limitations were significantly altered up to 24 months after depression assessment. The strength of these associations was similar to the figures obtained by Spijker et al[41] with the 36-item Short Form Health Survey in individuals with major depression. Furthermore, we found a significant negative association between CES-D scores as a continuous measure and later functioning, suggesting that, as previously reported,[6] these impairments in functioning were associated with the severity of depressive symptoms.

This study also confirms and extends in a general population sample the previously well-described associations between cognitive impairment (as measured by 3 cognitive tests)

and both depression[14–17] and altered functioning[12,13,22–26] (as measured by 2 functioning scores). However, despite these findings, this large population-based study did not support the hypothesis that cognitive dysfunction could substantially explain the association between depression and functioning. This negative result could be explained by the population-based design of our study, which excluded severely depressed participants. However, we found similar results with a more stringent definition of depression. Thus, these analyses did not provide additional evidence for a mediation effect of cognitive impairment. To our knowledge, only 1 large-scale study[30] found support for this hypothesis by formally testing the mediation. However, that study relied on subjective cognitive complaints that are poorly correlated with objective cognitive functions such as those measured by standardized neuropsychological tests.[47] Some studies[12,13] have reported an association between objectively assessed cognitive function and functional impairment in individuals with depression, thus providing preliminary evidence for a mediating role of cognitive function, but such mediation effect was not reported. Furthermore, since depression is associated with both cognitive and functional impairment, the association between objectively assessed cognitive function and functional impairment could have been confounded by depression itself.

Consistent with this alternative hypothesis, and contrasting with the lack of evidence for a mediating role of cognitive function, the mediation analyses suggested that depression could explain up to 44% of the relationship between cognitive deficits and altered functioning. Our results suggest that depression and cognitive impairment are strongly interrelated and both negatively impact functioning. However, depression without cognitive impairment may alter functioning to a greater extent than cognitive impairment without depression in a general population sample. Another plausible interpretation of this result is that depression might cause both cognitive and functional impairment. For instance, depression may result in both cognitive and functional impairment through altered motivation or decreased self-efficacy. Depression may also simultaneously affect cognitive and functional impairment, but by different mechanisms. For instance, ruminative thoughts associated with depression may reduce cognitive resources during performance of externally oriented cognitive tasks,[48] whereas poor self-esteem and embarrassment may have detrimental impact on social functioning.[30] However, these findings are controversial. For example, in 117 remitted patients with major depressive disorder, no association was found between residual symptoms such as self-blaming, feeling worthless, or hopeless and impaired cognition.[49] As mediation and confounding are identical statistically, they can be distinguished only on conceptual grounds, even in longitudinal studies.[50] Therefore, strictly speaking, our results are also consistent with the hypothesis that depression could mediate, rather than confound, the association between cognitive and functional impairment. For instance, the DSST, TMT-B, and SVF outcomes might result from impaired cognitive control, which is also involved in poor emotion regulation and thus vulnerability to depression.[48] Although these 2 hypotheses (ie, confusion versus mediation) are not mutually exclusive, they both imply that the impact of depression on functional impairment is independent of cognitive impairment.

In adults aged 45 years or older from the general population, the association between depression at baseline and role limitations and social functioning at follow-up could not be explained by lower scores on cognitive tests. Although the management of cognitive impairment associated with depression is central to the treatment of depression, it may not be sufficient to improve the functioning beyond what is expected from the improvement of depression per se at the general population level. Further studies based on more ecological cognitive tests (eg, tests involving social cognition or integration of cognitive tests in social context), but also using objective measures of functioning (eg, absenteeism), are needed to further refine our understanding of the mechanisms explaining why depression is one of the most disabling conditions worldwide.[51]

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Supplementary Material

Article Title: Depression, Cognitive Functions, and Impaired Functioning in Middle-Aged Adults From the CONSTANCES Cohort

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Appendix 1

Assessment of depressive symptoms

The CES-D consists of 20 items that are designed to measure self-reported depressive symptoms during the week prior to the test [1] with adequate internal consistency (Cronbach's alpha: 0.88 in the current sample). The total score ranged from 0 (no depressive symptom) to 60. We used a cut-off score of 19 (CES-D score ≥19 versus <19) to define depression status, according to the validation study of the French version of the CES-D (sensitivity/specificity for the diagnosis of major depression: 0.853/0.859) [2].

Assessment of cognitive functions

The DSST is a subtest of the Wechsler Adult Intelligence Scale-Revised, a timed paper- and pencil- task that measures psychomotor speed, sustained attention and logical reasoning [3]. It consists of matching symbols with their corresponding numerical digit as fast as possible. The DSST score represents the number of correctly matched symbols in 120 seconds. TMT-B requires to draw lines sequentially connecting alternatively encircled numbers and letters (e.g., 1, A, 2, B, 3, C, etc.) distributed on a sheet of paper [4]. The TMT-B score represents the amount of time required to complete the task. SVF requires participants to say as many words as possible from the "Animal" category in 60 seconds [5].

Assessment of functioning

The SF-12v2 is a widely used measure of health-related quality of life, with adequate reliability and validity [6-8]. It measures eight health aspects, namely general health, physical functioning, role limitations due to physical health problems, bodily pain, vitality, social functioning, role limitations due to emotional problems, and mental health. Mental health and

vitality subscales were not taken into account because of their obvious overlap with CES-D items ("Did you have a lot of energy?", "Have you felt downhearted and depressed?"). Because we were interested in functional impairment associated with depression specifically, we a priori decided to use two subscales as primary outcomes [9]: role limitations due to emotional problems and social functioning. These three items were rated from 1 (“All of the time”) to 5 (“None of the time”), leading to a score from 2 to 10 for role limitations and from 1 to 5 for social functioning [9]. For both scales, a higher score corresponds with a better functioning. Role limitations due to emotional problems, henceforth referred to as “role limitations”, was assessed with two items: "During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? 1) Accomplished less than you would like, 2) Did work or other activities less carefully than usual". Social functioning was assessed with one item: "During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?"). These three items were rated from 1 (“All of the time”) to 5 (“None of the time”), leading to a score from 2 to 10 for role limitations and from 1 to 5 for social functioning [9]. For both scales, a higher score corresponds with a better functioning.

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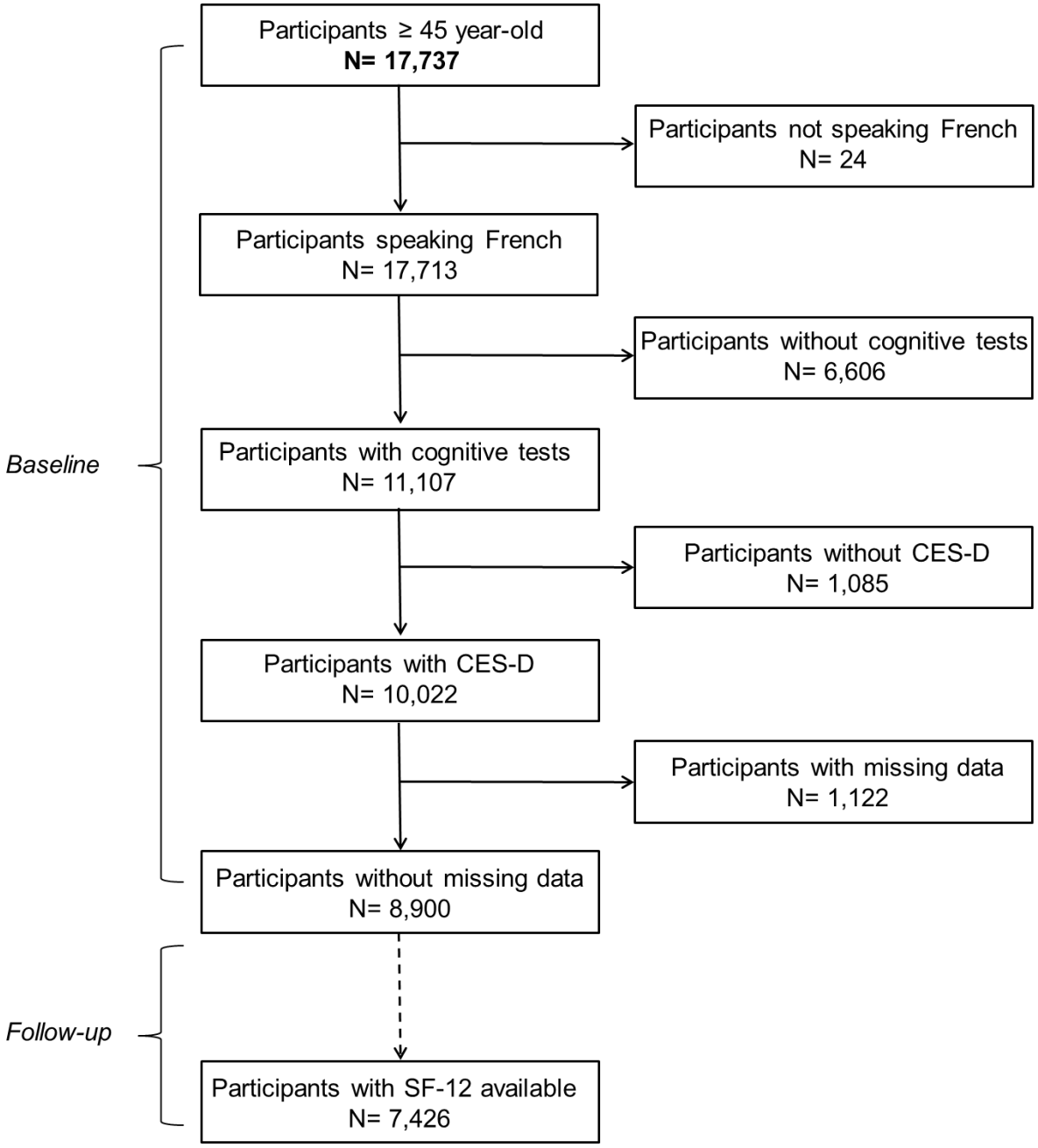
Supplementary Figure 1. Flow chart of the study population selection



Supplementary Table 1: Characteristics of participants according to depression status (N=7426)

	Depression status (CES-D score <19) N=6443		Depression status (CES-D score ≥19) N=983			
Continuous variables	**mean**	**sd**	**mean**	**sd**	**t**	**p**
Age	57.91	7.24	57.03	6.88	-3.70	<0.001
N of days between inclusion and FU	497.47	158.52	497.47	148.74	0.03	>0.99
CES-D score	7.34	4.91	26.56	6.95	83.53	<0.001
DSST score	67.55	14.99	65.48	15.62	-3.89	<0.001
TMT-B score	66.79	31.39	70.78	32.69	3.59	<0.001
SVF score	23.92	5.78	23.18	5.75	-3.78	<0.001
Role limitations	8.73	1.59	6.70	1.93	-31.56	<0.001
Social functioning	4.26	0.83	3.29	0.95	-30.37	<0.001
Discrete variables	**N**	**%**	**N**	**%**	**χ^2**	**p**
Sex					115.17	<0.001
Men	3238	50.26	313	31.84		
Women	3205	49.74	670	68.16		
Date of inclusion					1.11	0.29
2012	1046	16.23	146	14.85		
2013	5397	83.77	837	85.15		
Education level					30.77	<0.001
No diploma	103	1.60	27	2.75		

Lower secondary education	513	7.96	99	10.07		
Professional education	1207	18.73	203	20.65		
Upper secondary education	1104	17.13	197	20.04		
Bachelor	1477	22.92	211	21.46		
Fourth year university level	658	10.21	88	8.95		
Master degree or higher	1174	18.22	134	13.63		
Other	207	3.21	24	2.44		
Alcohol intake					53.38	<0.001
Never	189	2.93	45	4.58		
≤1glass/month	714	11.08	179	18.21		
2-3glasses/month	1224	19.00	187	19.02		
≥1glass/week	4316	66.99	572	58.19		
Life cannabis use					2.10	0.35
Yes	1140	17.69	192	19.53		
No	5263	81.69	786	79.96		
No intent to answer	40	0.62	5	0.51		

CES-D: Center for Epidemiologic Studies Depression Scale; DSST: Total score for Digit Symbol Substitution Test; TMT-B: Total time for Trail Making Test B, SVF: Semantic Verbal Fluency; FU: follow-up; sd: standard deviation; χ^2: chi-square value; t: t value.

Supplementary Table 2: Characteristics of lost to follow-up participants and comparisons with the study population

	Participant status					
	Included in the study N=7426		Lost to follow-up N=1474			
Continuous variables	**mean**	**sd**	**mean**	**sd**	**t**	**p**
Age	57.80	7.20	57.19	7.23	-2.93	0.003
CES-D score	9.88	8.35	12.28	10.05	8.60	<0.001
DSST score	67.27	15.09	62.88	15.31	-10.08	<0.001
TMT-B score	67.32	31.60	75.38	38.20	7.60	<0.001
SVF score	23.82	5.78	22.51	5.76	-7.99	<0.001
Discrete variables	**N**	**%**	**N**	**%**	**χ^2**	**p**
Sex						
Men	3551	47.82	743	50.41	3.20	0.07
Women	3875	52.18	731	49.59		
Date of inclusion						
2012	1192	16.05	251	17.03	0.79	0.37
2013	6234	83.95	1223	82.97		
Education level						
No diploma	130	1.75	81	5.50	143.23	<0.001
Lower secondary education	612	8.24	195	13.23		
Professional education	1410	18.99	317	21.51		
Upper secondary education	1301	17.52	229	15.54		

Bachelor	1688	22.73	290	19.67		
Fourth year university level	746	10.05	102	6.92		
Master degree or higher	1308	17.61	204	13.84		
Other	231	3.11	56	3.80		
Alcohol intake					0.90	0.82
Never	234	3.15	44	2.99		
≤1glass/month	893	12.03	179	12.14		
2-3glasses/month	1411	19.00	266	18.05		
≥1glass/week	4888	65.82	985	66.82		
Life cannabis use					4.61	0.10
Yes	1332	17.94	274	18.59		
No	6049	81.46	1184	80.33		
No intent to answer	45	0.61	16	1.09		

CES-D: Center for Epidemiologic Studies Depression Scale; DSST: Total score for Digit Symbol Substitution Test; TMT-B: Total time for Trail Making Test B, SVF: Semantic Verbal Fluency; FU: follow-up; sd: standard deviation; χ^2: chi-square value; t: t value.