Longitudinal Analysis of the Association between Depressive Symptomatology and Cognitive Deterioration

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Although many studies have found a cross-sectional relation between depression and dementia or depressive symptomatology and cognitive functioning, the direction of the association is still unknown. The purpose of this analysis was to determine whether high depressive symptomatology is predictive of cognitive deterioration among the elderly 3 years later. Data came from a community-based prospective cohort study of noninstitutionalized and nondemented subjects aged 65 years and over living in the Gironde department in southwest France (1,600 subjects were interviewed at both study entry in 1989 and 3-year follow-up). Cognitive functions were assessed with the Mini-Mental State Examination (MMSE), and cognitive deterioration was defined as an MMSE score decrease of at least five points between two assessments. The Center for Epidemiologic Studies Depression (CES-D) Scale was used to evaluate the level of depressive symptomatology. The present study reports that a high level of depressive symptomatology is not predictive of cognitive deterioration 3 years later (relative risk = 0.8, 95% confidence interval 0.3–2.1). The authors observed that the risk of cognitive deterioration was associated with the concomitant level of depressive symptomatology at the 3-year follow-up, independent of depressive symptoms at entry. These results indicate that the association between high depressive symptomatology and poor cognitive functioning is cross-sectional, and they illustrate the importance of adjusting for depressive symptomatology in epidemiologic studies assessing cognitive functions. Am J Epidemiol 1996;144:634–41.

For many years, clinical studies have suggested that the simultaneous occurrence of depressive disorders and dementia in elderly individuals was more frequent than expected as a result of random coincidence (1–4). Reifler et al. (1) reported a diagnosis of depression in 23 percent of cognitively impaired geriatric outpatients, whereas they reported the prevalence of major depressive disorder to be 4 percent in community samples of the equivalent age group. Similarly, several epidemiologic surveys of large community samples have found a significant cross-sectional association between high depressive symptomatology and poor cognitive functioning (5–11).

While it is accepted that there is an association between depression and cognitive functioning, the nature of the relation remains unclear. It is not known whether depressive disorders precede cognitive deterioration or, conversely, whether depressive symptoms occur after cognitive impairment. According to the former assumption, depression might be a risk factor for dementia. Jorm et al. (12) reanalyzed several published case-control studies and concluded that depression was a risk factor for the late onset of Alzheimer’s disease.

Low cognitive functioning is not synonymous with dementia. Some cognitive decline is part of normal aging (13–15), and the rate of decline is variable in both normal and pathologic aging. Depressive symptoms may predict cognitive change and may alter the rate of decline. In order to delineate normal aging from the more pathologic process, we have chosen to differentiate cognitive deterioration from cognitive decline. We define cognitive deterioration as a rapid decline in cognitive function, and, in this study, we investigate longitudinally whether there is an increased risk of cognitive deterioration for elderly persons with a high level of depressive symptoms.

MATERIALS AND METHODS

Study sample

The analyses presented here use longitudinal data from a community-based sample of noninstitutional-
ized men and women aged 65 years and over, living in Gironde, in the Southwest of France. This study is part of the PAQUID research program. The PAQUID cohort is a stratified (age, sex, size of town) sample, and it has been described elsewhere (16). The survey started in 1988, and subjects have been interviewed at 1 year and then every 2 years. At each wave, trained psychologists interviewed subjects in their home. For the analyses reported here, we have used data at study entry and data from the 3-year follow-up interviews. We excluded subjects with a confirmed diagnosis of dementia according to the neurologist’s assessment at study entry (n = 66). At the first wave, 2,726 non-demented persons were interviewed. Three years later, 1,600 of them were reinterviewed, 311 subjects had died during the interval, 800 refused to be reinterviewed, and 15 were lost to follow-up. In the present study, we classified persons lost to follow-up with those who refused to be reinterviewed.

Measurements

Cognitive performance was assessed with a battery of neuropsychologic tests. The present results are based on a summary screening instrument, the Mini-Mental State Examination (MMSE) (17). The MMSE is a neuropsychologic scale widely utilized as a screening instrument for cognitive impairment and dementia in both epidemiologic studies and in clinical practice. It consists of 18 items that evaluate different domains of cognitive functioning, including orientation in time and space, short-term memory, data recording, concentration, mental arithmetic, language, and motor activity. Each correct answer is scored as one point, so that the total score ranges from 0 to 30. A cutoff of 23/24 is widely used as an indicator of cognitive deficit (18, 19).

The outcome of interest in the present study, change in cognitive function, was calculated as the difference in the MMSE score between study entry and 3-year follow-up. The mean difference in the MMSE score was 0.33 (improvement), and the corresponding standard deviation was 2.58. We defined cognitive deterioration as a drop of five points or more between the baseline and follow-up. This choice was based on an empiric rule frequently used in psychometrics that consists in considering as “pathological” a subject whose score is less than the average score minus two times the standard deviation (20). Longitudinal studies on change in cognitive performance are still rare, and no other criteria have been established to define cognitive deterioration.

Depressive symptomatology was measured by the Center for Epidemiologic Studies Depression (CES-D) Scale, developed by Radloff (21) in 1977. The CES-D Scale has been widely used in epidemiologic studies and has been shown to be appropriate for use in studies with the elderly (22–24). It consists of 20 self-report items concerning symptoms and feelings experienced during the preceding week. Each item is scored from 0 to 3 according to the frequency of the symptom. The higher the score, the higher the level of depressive symptomatology. Evaluation of the CES-D score in a French population showed that men and women scoring more than 16 or 22, respectively, should be considered at high risk for clinical depression (25).

Data analysis

Logistic regression models (26) were used to examine variables associated with cognitive deterioration. Only subjects whose cognitive performance was assessed at both the beginning and at 3-year follow-up were included in the analyses.

The potential confounders we studied were sex, age, marital status, educational level, and level of physical impairment because of their demonstrated association with both depressive symptomatology and cognitive functions in cross-sectional analyses (10). The level of physical impairment was assessed with the Instrumental Activities of Daily Living (IADL) Scale developed by Lawton (27).

RESULTS

The characteristics of the full cohort at study entry are described in table 1. The proportion of women was 60 percent, and women were older than men with a mean age of 75.3 years (standard deviation, 7.1) versus a mean age of 74.0 years (standard deviation, 6.5); p < 0.001. A large proportion of the sample was widowed, and more than 60 percent of the subjects had the equivalent of, or less than, a primary level of schooling.

The baseline characteristics of subjects included in the analyses (n = 1,600) were compared with those of subjects who had refused to participate at the third wave (n = 800) or were lost to follow-up (n = 15) (table 1). These 815 subjects had significantly lower levels of education and cognitive performance but higher levels of physical impairment. The proportion of women among those who refused was higher. No significant differences were observed for the other covariates, including high depressive symptomatology. In contrast, compared with the 1,600 subjects included in the analysis, the subjects who died during the interval (n = 311) were more often men, older, and more frequently widowed and had a lower educational level; they were also more frequently physically or
cognitively impaired and had a higher level of depressive symptomatology.

We observed significant and very stable cross-sectional associations between the level of depressive symptomatology and cognitive function. At both time points, a high level of depressive symptomatology was associated with a higher risk (odds ratio = 2.6) of cognitive impairment (table 2). Similarly, the correlation between the CES-D and MMSE total scores was $r_{10} = -0.24$ ($p < 0.001$) at study entry and $r_{13} = -0.26$ ($p < 0.001$) at 3-year follow-up for subjects interviewed at both time points.

The mean change score for the MMSE was 0.3 (standard deviation, 2.6), indicating a small improvement in cognitive performance. The range of change score was from −20 to 10, and the quartile values were −1, 0, and 2. A decrease of five points or more on the MMSE score between the beginning of the study and the 3-year follow-up was observed for 3.1 percent ($n = 48$) of the subjects. The crude and adjusted associations between cognitive deterioration and the covariates are presented in table 3. Between study entry and follow-up, the incidence of cognitive deterioration was greater among women, the widowed,
and never married and increased significantly with age ($p < 0.001$), level of physical disability ($p < 0.001$), and decreasing levels of education. The percentage of subjects who deteriorated did not differ according to the entry level of depressive symptomatology.

To assess the possible confounding effects that could mask the CES-D/cognitive deterioration relation, we performed a multivariate analysis. We used multiple logistic regression analysis to adjust for the baseline MMSE score and variables related to both the CES-D and MMSE scores (10). Results were comparable with those described for the univariate analysis. An initial high level of depressive symptomatology was not a risk factor for cognitive deterioration 3 years hence (relative risk = 0.8, 95 percent confidence interval 0.3–2.1). This result persisted when the data were stratified for sex. Furthermore, there were no interaction effects between education or functional impairment and the other covariates.

To understand the meaning of the cross-sectional relations observed between depressive symptomatology and cognitive functions, we examined whether their longitudinal variations were correlated by studying the association between cognitive change ($\text{MMSE}_{\text{3-year follow-up}} - \text{MMSE}_{\text{at study entry}}$) and change in the CES-D total score adjusted on the same potential confounders (multiple linear regression analysis). We found a significant linear association between change in cognitive performance and change in depressive symptomatology ($\beta = -0.026$, 95 percent confidence interval −0.039 to −0.013; $p < 0.001$). This association was found at both levels of cognitive functioning (above and below 24 on MMSE score at study entry).

Table 4 examines the relations between changes of depressive symptomatology level (dichotomized as above and below threshold) and the incidence rate of cognitive deterioration. The incidence rate of cognitive deterioration among subjects with high levels of depressive symptomatology at both entry and 3-year follow-up was 5.3 percent and did not differ from the 4.4 percent rate for subjects with a high level of depressive symptomatology only at 3-year follow-up (chi-square = 0.05, $p = 0.8$, 1 df). Similarly, the rate of cognitive deterioration did not differ significantly between subjects with low levels of depressive symptomatology at both entry and 3-year follow-up (2.3 percent) and those with a high level of depressive symptomatology only at the first wave (0.9 percent) (chi-square = 1.0, $p = 0.5$, 1 df). These findings suggest that the rate of cognitive deterioration is essentially associated with the level of depressive symptomatology at the third wave.

The relatively high proportion of nonrespondents (34 percent of living subjects) at the 3-year follow-up could be a potential source of selection bias, though the proportion was equivalent for those with high and low levels of depressive symptoms. To confirm whether selection bias would affect the results, we carried out a sensitivity analysis; we hypothesized that individuals who were depressive at study entry and who deteriorated in their cognitive abilities were more likely to refuse participation. We assumed that all the depressive nonrespondents had participated, and we progressively increased the proportion of cognitive deterioration among the depressive nonrespondents. Our results showing no association with depressive symptoms persisted until we assumed that 10 percent of depressive nonrespondents had deteriorated as compared with the observed 2.8 percent deterioration among the depressive respondents. The hypothesized incidence among depressive subjects was 5.5 percent and significantly higher than the incidence of 3.0 percent for the nondepressive respondents (chi-square = 4.4, $p = 0.04$, 1 df). This assumption is highly con-
TABLE 3. Incidence of cognitive deterioration and crude and adjusted risk estimates for selected factors, PAQUID program, Gironde, France, 1989–1992

<table>
<thead>
<tr>
<th>No.</th>
<th>Incidence rate/100</th>
<th>RR†</th>
<th>95% CI†</th>
<th>RR‡</th>
<th>95% CI‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>639</td>
<td>1.9</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>913</td>
<td>3.9</td>
<td>2.3</td>
<td>1.1–4.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–74</td>
<td>856</td>
<td>0.9</td>
<td>1.0</td>
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<td>1.0</td>
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<tr>
<td>75–84</td>
<td>575</td>
<td>4.9</td>
<td>4.9</td>
<td>2.2–11.0</td>
<td>4.2</td>
</tr>
<tr>
<td>≥85</td>
<td>121</td>
<td>9.9</td>
<td>11.3</td>
<td>4.5–28.3</td>
<td>8.0</td>
</tr>
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<td>Marital status</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>895</td>
<td>2.0</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Widowed</td>
<td>518</td>
<td>4.0</td>
<td>1.9</td>
<td>1.0–3.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Never married</td>
<td>83</td>
<td>9.6</td>
<td>5.5</td>
<td>2.3–13.1</td>
<td>3.2</td>
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<tr>
<td>Divorced/separated</td>
<td>48</td>
<td>2.1</td>
<td>1.0</td>
<td>0.1–7.9</td>
<td>—</td>
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<tr>
<td>Education</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Secondary/baccalaureate/ university degree</td>
<td>422</td>
<td>2.0</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
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<tr>
<td>Primary with diploma</td>
<td>496</td>
<td>3.0</td>
<td>1.7</td>
<td>0.8–3.8</td>
<td>1.8</td>
</tr>
<tr>
<td>No school/primary without diploma</td>
<td>553</td>
<td>5.2</td>
<td>2.8</td>
<td>1.3–6.1</td>
<td>2.5</td>
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<tr>
<td>Functional autonomy§</td>
<td></td>
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<td></td>
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<td>No limitation</td>
<td>1,202</td>
<td>2.4</td>
<td>1.0</td>
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<tr>
<td>One limitation</td>
<td>154</td>
<td>6.5</td>
<td>3.6</td>
<td>1.7–7.6</td>
<td>2.3</td>
</tr>
<tr>
<td>≥2 limitations</td>
<td>191</td>
<td>7.3</td>
<td>3.8</td>
<td>1.9–7.6</td>
<td>2.1</td>
</tr>
<tr>
<td>Depressive symptomatology‖</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below threshold</td>
<td>1,358</td>
<td>3.0</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Above threshold</td>
<td>182</td>
<td>2.8</td>
<td>0.8</td>
<td>0.3–2.2</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* Subjects' numbers may be less than the total because of missing values.
† RR†, crude relative risk; CI, confidence interval; RR‡, relative risk adjusted for all other variables and the baseline total score on the Mini-Mental State Examination.
‡ The risk ratio and confidence interval are not reported because the cell sample size was too small to provide estimates.
§ Measured by the Instrumental Activities of Daily Living (IADL) Scale.
‖ Measured by the Center for Epidemiologic Studies Depression (CES-D) Scale; a score above threshold is indicative of a high level of depressive symptomatology (≥17 for men, ≥23 for women).

TABLE 4. Incidence of cognitive deterioration by depressive symptoms at study entry and 3 years of follow-up, PAQUID program, Gironde, France, 1989–1992

<table>
<thead>
<tr>
<th>Depressive symptomatology as assessed by CES-D* Scale</th>
<th>At entry</th>
<th>At 3-year follow-up</th>
<th>No. of subjects</th>
<th>% of subjects with cognitive deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below threshold‖</td>
<td>1,234</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below threshold‖</td>
<td>90</td>
<td>4.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above threshold‖</td>
<td>116</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above threshold‖</td>
<td>57</td>
<td>5.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CES-D, Center for Epidemiologic Studies Depression.
† A score above threshold is indicative of a high level of depressive symptomatology (≥17 for men, ≥23 for women).

DISCUSSION

This longitudinal survey of a large community-based sample of elderly individuals provides evidence that a high level of depressive symptomatology was not a risk factor of cognitive deterioration. The number of incident cases of dementia was too small to examine whether depressive symptoms were predictive of dementia. However, as demented patients constitute a subgroup of those who deteriorated, our findings do not seem to suggest that depressive elderly individuals have a marked increased risk of dementia.

The strong cross-sectional association between depressive symptomatology and cognitive performance contrasts with the absence of a longitudinal relation between these two variables. In addition, 3-year changes of cognitive scores were significantly correlated with the simultaneous evolution of depressive symptoms.
symptoms. Elaborate test batteries (28) have demonstrated that depressive illness was associated with some degree of cognitive deficits. Our data show that in elderly subjects very simple neuropsychologic tests can reveal this deficit. Hence, one can wonder whether to improve diagnosis and treatment of depression in elderly subjects would have positive consequences on their cognitive functioning. However, preliminary data suggest that, among those with a depressed mood, the incidence rate of cognitive deterioration is higher in individuals taking psychotropic drugs than in those who do not (results not shown). It could be that the medication is affecting cognitive performance or that psychotropic treatments are a marker of the severity of depressive symptoms. As these different hypotheses have specific public health implications, further epidemiologic surveys that include duration and dosage levels of psychotropic drug use are needed to clarify this issue.

Our results argue that a measure of depressive symptomatology is necessary in all cross-sectional or prospective epidemiologic studies assessing cognitive decline. Our findings also have potential implications for clinical trials in demented and cognitively impaired patients. To avoid misinterpretation of clinical trial results, it is advisable not only to exclude patients with a clinical diagnosis of depression, as is usually done, but also to assess carefully the initial and final levels of depressive symptomatology of the patients included in the trial.

In addition to the findings that were directly related to our main objectives, the present study has another salient result. The effect of education on cognitive performance has been subjected to much debate surrounding the issue that fewer years of education may be a risk factor or test bias (29–31). In the present study, we examined the difference between a repeated measure of cognitive function, which should partially eliminate an education-related effect on the cognitive tests. If we assume that educational level does not have an effect on training due to repeated testing, our results are consistent with previous findings reporting the effect of education on cognitive change (32, 33).

Several methodological issues must be raised. The first one concerns the validity of our measure of cognitive deterioration. On average, subjects slightly improved their cognitive performance over the 3-year period, whereas a decline was expected as part of normal aging. Regression toward the mean could explain in part this result. Another possible explanation is a training effect. Indeed, at 3-year follow-up, subjects were being assessed for at least the second time with the MMSE, and we cannot exclude the possibility that they remembered some of the items and the corresponding answers. The MMSE total score increase could also be explained by a stress effect at the first assessment that disappeared at subsequent interviews.

Another concern is the robustness of our findings for different definitions of cognitive deterioration. Sensitivity analyses showed that using a change of four or six points in MMSE scores to define cognitive deterioration did not modify significantly our findings. Furthermore, when change in cognitive function was studied as a continuous outcome, the overall results remained the same.

A further methodological issue concerns possible selection bias at 3-year follow-up related to attrition due to mortality or nonresponse (34–36). Several studies have observed an association between cognitive functions and survival (37–41). Based on these reports, we may speculate that, among the people who died, we would have observed some cognitive deterioration for many of them. This issue was especially important because depressive symptomatology at entry was higher in subjects who died than in those who survived. When deceased individuals were combined with the cognitively deteriorated, reanalysis did not show any relation between the initial level of depressive symptomatology and cognitive deterioration or death (risk ratio = 1.2, 95 percent confidence interval 0.8–1.8). Some selection bias may affect our result, but even if high depressive symptomatology were predictive of cognitive deterioration, the effect would be quite weak.

A final issue concerns the measurement of depressive symptomatology. The CES-D Scale evaluates the presence of depressive symptoms over a 1-week period, and a high CES-D score is predictive of clinical depression but not synonymous with it. The depressive symptoms may be of longer duration or may be a transient state and then have no, or limited, predictive importance. However, subjects with high levels of depressive symptomatology at both entry and 3-year follow-up did not have an increased risk of cognitive deterioration (table 5). One possible explanation may be that the measure of depressive symptoms is too distant from the assessment of cognitive change, and therefore the predictive value of the CES-D may be compromised or diminished. In order to verify whether the time span between the two assessments was too long, we performed the equivalent analysis to examine the relation between depressive symptomatology at study entry and cognitive change at 1-year follow-up, as well as depressive symptomatology at 1-year follow-up and cognitive change at 3-year follow-up. We found no association for either analysis, which suggests that the time lag we used does not alone explain the absence of a predictive association.

In conclusion, this study suggests that high depressive symptoms are not predictive of cognitive deterioration. To our knowledge, our study is the first to examine this relation, and other studies will be needed to confirm or negate our findings. The association between high depressive symptomatology and poor cognitive functioning appears to be only cross-sectional. These results show the usefulness of taking into account the level of depressive symptomatology when measuring cognitive performance in the elderly in clinical practice, epidemiologic surveys, and clinical trials.

ACKNOWLEDGMENTS

This research was supported by the Fondation de France, Paris, France; Sandoz Laboratories, Paris, France; Pêchiney, Paris, France; Danone, Paris, France; Axa Insurance Group, Paris, France; the Conseil Général de la Dordogne; the Ministère de la Recherche et de la Technologie; the Caisse Nationale d’Assurance Maladie; the Caisse Primaire d’Assurance Maladie de Dordogne; the Mutualité Sociale Agricole de Gironde et Dordogne; the Conseil Régional d’Aquitaine; 2010 Media, Paris, France; Capimmec; and the direction Régionale des Affaires Sanitaires et Sociales d’Aquitaine. The work of C. Dufouil was supported by the Fondation de France.

REFERENCES