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Prevalent and incident depression in community-dwelling elderly persons with diabetes mellitus: results from the ZARADEMP project

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Abstract

Aims/hypothesis Although several studies have reported on the association between diabetes and depression, none have used both formal psychiatric criteria and a prospective, population-based design. Therefore, it remains unclear whether diabetes is a risk factor for the development of depression. Moreover, it is not clear if this effect is influenced by other chronic diseases and functional disabilities.

Methods A large ($n=4,803$) representative community-based study in Spanish elderly subjects (at least 55 years of age) was conducted. The presence of major depression was assessed by means of a standardised psychiatric diagnostic interview (Automated Geriatric Examination for Computer Assisted Taxonomy). Subjects underwent a

baseline assessment and a follow-up assessment after 2 and 5 years to determine the incidence of depression.

Results At baseline 597 subjects (12.5%) were identified as having diabetes. Prevalence and incidence of depression in cases of diabetes were 15.4% and 16.5% respectively. Diabetes was associated with an increased risk of prevalent (odds ratio [OR]=1.47; 95% CI: 1.16–1.83) and incident (OR=1.40; 95% CI: 1.03–1.90) depression. Controlling for potential confounders did not essentially change these findings (prevalent depression: OR 1.41, 95% CI: 1.08–1.83; incident depression: OR 1.26, 95% CI: 0.90–1.77).

Conclusions/interpretation In a large, representative prospective population-based sample using strict psychiatric criteria, we confirmed previous findings that diabetes is associated with an increased risk of depression. The effect on the incidence of depression suggests that diabetes may play a role in the development of depression in the elderly. The presence of comorbid medical diseases seems to decrease the effects of diabetes on the risk of prevalent depression, but to increase the risk of incident depression.

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Keywords Community · Depression · Diabetes · Elderly · Epidemiology

Abbreviations

AGECAT automated geriatric examination for computer assisted taxonomy
DSM-III diagnostic and statistical manual of mental disorders, 3rd edition
GMS geriatric mental state
IADL instrumental activities of daily living
OR odds ratio

Introduction

Depression is a disorder with many adverse consequences, including impaired physical capability [1], worsened adjustment to somatic illness [2], and even increased risk of (non-suicidal) death [3]. In patients with diabetes mellitus, depression has been associated with worsened glycaemic control [4, 5], non-adherence to treatment [6], and increased risk of vascular complications, including diabetic retinopathy, nephropathy, neuropathy and macrovascular complications [7]. Several studies have suggested that depression is a risk factor for mortality in diabetes patients [8–10], although this has not been confirmed by others [11].

The prevalence of comorbid depression in adults with diagnosed type 1 and type 2 diabetes has been assessed in several studies, which were summarised in 1993 [12] and in 2001 [13]. The latter study [13] confirmed that type 1 or 2 diabetes doubles the risk of comorbid depression. Since most of the studies included in this meta-analysis were uncontrolled or did not have an optimal control group, a community-based study was conducted [14]. In this study, an association between diabetes and depression was found when comparing diabetic patients who were comorbid for other chronic disease both with non-diabetic control subjects with other chronic diseases, and with diabetic patients who had no other chronic conditions.

Two limitations to the study by Pouwer et al. [14] prompted us to conduct a new study with some alterations in study design. (1) Pouwer et al. used the term ‘pervasive depression’ to denote a positive score on a self-report questionnaire, whereas the diagnosis of treatable depression should be based on a formal psychiatric interview. For example, the available intervention trials [15–17] are all based on a formal psychiatric interview using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition (DSM-III). Clinical guidelines for the treatment of depression in the medically ill are also based on formal diagnostic criteria. As an indication of how the assessment of depression affects the estimated prevalence, Anderson et al. [13] found a prevalence of 11.4% based on formal psychiatric criteria and of 31.0% based on self-report scales ($p < 0.0001$). In the present study we therefore used formal psychiatric criteria of depression. (2) The question of whether diabetes is a risk factor for depression can only be addressed in a prospective study assessing incident rather than prevalent depression. Although several recent studies have assessed the potential role of diabetes in the development of depression [18–21], these studies either did not use formal psychiatric criteria or did not use a prospective, population-based design. We therefore not only studied the association of diabetes with prevalent depression, but also assessed incident depression at 2- and 5-year follow-up.

As in the study by Pouwer et al. [14], the increased risk of depression was established only in the presence of other comorbid chronic somatic illness, we explicitly tested the effects of the presence of chronic comorbidities. As they had also hypothesised that functional limitations often accompanying chronic comorbidities could play an essential role in the development of depression in diabetes, we also tested and controlled for the covariate effects of disability on the prevalence and incidence of depression.

Subjects and methods

Sample

Data are from the Zaragoza Dementia and Depression (ZARADEMP) study. Data collection and sample characteristics have been described elsewhere [22, 23]. In short, a random sample, stratified by sex and age, of community-dwelling persons aged at least 55 years was drawn from the census list of the city of Zaragoza (Spain) in 1991. The Helsinki convention principles were adhered to throughout the study, including provision of written informed consent, privacy, confidentiality and security, according to Spanish Law.

From an original sample of 9,739 patients, it was found that 3.6% had moved away, 18.9% had died and 7.6% were untraceable. In addition, 20.5% refused participation. As a result, 4,803 subjects underwent the baseline interview, starting in 1994 (Wave I).

After approximately 2 (Wave II) and 5 years (Wave III), follow-up assessments of the surviving, non-demented elderly were conducted. Of the 4,803 patients originally included, 3,237 (67.4%) participated in Wave II, with 2,403 of these (74.2%) participating in Wave III. The main reasons for drop-out at the two follow-up assessments were: refusal (9.9% and 9.3% respectively), death (7.0% and 9.2% respectively), untraceable (1.8% and 3.3% respectively) and moved away (1.6% and 2.1% respectively) [24].

Assessments

A 25–90-min interview was conducted at the subjects’ homes by well-trained and regularly supervised lay interviewers. The interview included the standardised Spanish versions of the Mini-Mental State Examination (MMSE) [24, 25], the Geriatric Mental State (GMS)-History and Aetiology Schedule- Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) package [26, 27], the Katz Index [28, 29], the Instrumental Activities of Daily Living (IADL) scale [30, 31], and a series of questions regarding medical and psychiatric history includ-

ed in the European Study on Dementia risk factors questionnaire [32]. All instruments have been validated in Spanish and have proven reliability. An identical interview was conducted at approximately 5 years of follow-up, with the interviewers unaware of the results of the baseline interview. Medical reports, which are commonly kept at home by Spanish patients and often include laboratory tests, were used to help in ascertaining the collected data.

Assessment of depression

Diagnosis of depression was based on the GMS interview, a semi-structured standardised clinical interview for assessing the mental state in elderly persons [26]. The AGE-CAT, a set of computer algorithms to analyse the GMS data, was applied to reach psychiatric diagnosis of depression. Diagnostic confidence levels 1 and 2 were classified as sub-threshold cases, while confidence levels of 3 or more have been proven valid for detecting cases of depression that require clinical attention in community samples [33]. In this study, the presence of depression was defined as GMS-AGE-CAT level 3 or higher. The reliability and validity (concordance with DSM-III-R diagnosis) of the Spanish version of the GMS-AGE-CAT procedure has been reported elsewhere [23]. Prevalent baseline depression was based on the first interview, while incident depression was based on the second interview (Wave II) and third interview (Wave III), excluding subjects with prevalent depression at baseline.

Presence of diabetes

The presence of diabetes was scored by assessing the medical history, by means of the following questions: (1) Do you have diabetes (sugar)? (2) Who diagnosed you as having diabetes? and (3) What kind of treatment did you receive for your diabetes? Only subjects responding positively to the first question and for whom the diagnosis was established by a medical doctor and who were receiving treatment (insulin, oral hypoglycaemic agent or diet) were regarded as having diabetes.

Covariates

Potentially confounding factors, assessed at baseline, included demographic variables (age, sex, marital status, education), cardiovascular risk factors (hypertension, smoking, statin use), comorbid medical illness, cognitive functioning and disability. Education level was classified as low (only primary school or less) or not low. Hypertension was measured by the average of two readings of blood pressure, classified as either systolic hypertension (systolic pressure ≥ 140 mmHg) or diastolic hypertension

(diastolic pressure >90 mmHg). Smoking was based on WHO criteria [34] for lifetime tobacco exposure and classified as smoker or non-smoker. Statin use was defined according to the Anatomical therapeutic chemical classification of the WHO [35] and included the use of B04 drugs (hypocholesterolaemics). Cardiovascular risk factors were included as potential confounders because the vascular depression hypothesis suggests that (part of) late-life depression is caused by cerebrovascular lesions due to prolonged atherosclerosis [36]. The presence of other chronic diseases was estimated by counting the number of medications currently prescribed to the subjects. Medication use has been found to be a reliable indicator of chronic illness [37]. To be counted as medication for a chronic somatic illness, it had to be one of the following: B01 (anti-thrombotic agents), B04 (hypocholesterolaemics), C01 (cardiac therapy), C02 (anti-hypertensives), C03 (diuretics), H03 (thyroid therapy), H04 (systemic hormonal preparations, excluding sex hormones and insulins), M01 (anti-inflammatory and anti-rheumatic products), M04 (anti-gout preparations), N04 (anti-Parkinson drugs), R03 (drugs for obstructive airway diseases). Moreover, the drug had to be taken daily, and had to be prescribed by a medical doctor. Insulin and psychotropic drugs were not counted.

The Spanish version of the MMSE (Examen Cognoscitivo Mini-Mental) [38] is a reliable and valid indicator of cognitive function in very widespread use. Efficiency coefficients and population norms very similar to the ones reported by Folstein et al. in the USA have been found in Zaragoza [22, 23]. The Katz Index [28, 29], which assesses the Basic Activities of Daily Living, and the IADL scale [30, 31] were successfully translated and validated in Spanish. Taken together, the Katz Index and IADL scale cover both basic and instrumental aspects of daily living, and thus describe the level of a subjects' disability. For this study, the Katz Index and IADL scale were dichotomised, distinguishing between disability and no disability.

Statistical analyses

To analyse the cross-sectional and prospective associations between diabetes and depression in relation to the presence of comorbidities, we compared the prevalence and incidence of depression between diabetic and non-diabetic patients. Differences between these groups on categorical data were tested by chi-square tests, and differences on variables with approximately normal distributions were tested with *t* tests. The magnitude of the association of diabetes with depression was estimated by odds ratios (ORs) and their 95% CIs, both in bivariate analyses and in multivariate analyses, while controlling for the covariates mentioned above. To study the specific hypothesis that the association is confounded by disability or comorbidity, we

repeated the logistic regression analyses with the addition of these variables and checked whether these variables accounted for the associations between diabetes and depression. To test whether the associations between diabetes and depression are affected by disability and comorbidity, we conducted stratified analyses based on the presence of disability and chronic diseases.

Results

Of the 4,803 subjects recruited in the study, 554 (11.5%) had prevalent depression at baseline (Wave I). At Waves II and III, remarkably similar prevalence rates were found: 360 (11.1%) and 268 (11.2%). Of the 4,249 subjects with no baseline depression, 2,889 (68.0%) had a complete Wave II assessment, and of these 231 (8.0%) had incident depression. Of the non-depressed baseline subjects, 2,158 also had a Wave III assessment (50.8%). Of these subjects, 189 (8.8%) had incident depression. Subjects with incident depression at Wave II or Wave III ($n=374$; 12.9%) were combined for the analyses, and were contrasted with subjects without incident depression ($n=2515$; 87.1%).

Based on the baseline data, 597 of 4,757 patients were classified as having diabetes (12.5%) and 4,160 as not having diabetes (87.5%). A group of 46 subjects was considered to constitute doubtful cases, and these subjects were excluded from further analyses. In Table 1, a comparison is made between diabetic and non-diabetic subjects.

Subjects with diabetes differed from non-diabetic counterparts with regard to education level, prevalence of hypertension and statin use. Prevalent major depressive episodes were present in 15.4% of the subjects with diabetes, which was significantly higher than in non-diabetic subjects (11.0%) ($\chi^2=9.9$; $p=0.002$). Incident depression was found in 16.5% of the subjects with diabetes but was significantly lower in subjects with no diabetes (12.4%) ($\chi^2=4.5$; $p=0.03$).

The magnitude of the associations between diabetes and depression are shown in Table 2. In bivariate analyses, subjects with diabetes had a 1.47 (95% CI: 1.16–1.88) increased risk of prevalent depression and a 1.40 (95% CI: 1.03–1.90) increased risk of incident depression when compared to non-diabetic subjects. After controlling for potential confounders, these associations were somewhat reduced, i.e. 1.41 (95% CI: 1.08–1.83) and 1.26 (95% CI: 0.90–1.77), respectively, but the association with prevalent depression remained statistically significant. The addition of disability and presence of chronic somatic disease did not essentially change the associations.

We conducted a series of secondary analyses to explore whether the findings are similar when restricted to subjects >65 years old. We did this because the GMS

Table 1 Comparison of subjects with and without diabetes by baseline characteristics and prevalent and incident depression

	Diabetes	No diabetes
<i>N</i>	597 (12.5%)	4160 (87.5%)
Demographics		
Mean age	73.4 (9.0)	73.5 (9.9)
Male sex	40.7%	42.5%
Married/partner	60.1%	58.2%
Low education	53.4%	46.4%**
Cardiovascular risk factors		
Hypertension	74.3%	66.7%**
Current smoking	32.9%	31.3%
Statin use	9.9%	4.7%**
Health status		
Cognitive functioning (MMSE)	28.4 (5.9)	28.7 (6.5)
Katz index-dependent	13.7%	12.7%
IADL-dependent	23.9%	20.5%
Depression		
Prevalent depression	15.4%	11.0%**
Incident depression	16.5%	12.4%*

Unless otherwise stated, values are mean (SD) * $p<0.05$; ** $p<0.01$

was originally designed for subjects older than 65 years, whereas in our sample a small minority of subjects was still in the age range of 60 to 65 years. These analyses resulted in largely comparable findings for both prevalent (OR unadjusted 1.50) and incident (OR unadjusted 1.29) depression.

To explore whether disability and the presence of other chronic somatic diseases modify the associations between diabetes and depression, we repeated the logistic regression analyses stratified by the Katz and IADL scores, and the presence of chronic disease (Table 3). The association of diabetes and prevalent depression was observed only in the absence of other chronic somatic diseases and disability. No clear pattern was observed with respect to incident depression, although we did note a trend for diabetes to be associated with incident depression in the presence of other chronic somatic diseases. However, the addition of interaction terms for diabetes with comorbidity and disability to the logistic regression models resulted in non-significant interaction effects, both for prevalent depression (diabetes \times comorbidity: $p=0.20$; diabetes \times instrumental disability: $p=0.31$; diabetes \times basic disability: $p=0.89$) and incident depression (diabetes \times comorbidity: $p=0.26$; diabetes \times instrumental disability: $p=0.88$; diabetes \times basic disability: $p=0.33$).

Discussion

We studied the cross-sectional and prospective associations of diabetes mellitus and major depression in a large,

Table 2 Risk of prevalent and incident depression for subjects with diabetes controlling for several confounders

	OR _{unadjusted}	OR _{model 1}	OR _{model 2}	OR _{model 3}
Prevalent depression	1.47 (95% CI: 1.16–1.88)	1.46 (95% CI: 1.14–1.87)	1.51 (95% CI: 1.17–1.95)	1.41 (95% CI: 1.08–1.83)
Incident depression	1.40 (95% CI: 1.03–1.90)	1.42 (95% CI: 1.04–1.93)	1.28 (95% CI: 0.91–1.79)	1.26 (95% CI: 0.90–1.77)

Model 1: controlling for age and sex

Model 2: controlling for model 1 +partner, education, hypertension, smoking, statin use and cognitive functioning

Model 3: controlling for model 2 +Katz index, IADL and presence of chronic somatic disease

community-based sample of elderly subjects. We compared the prevalence and incidence of depression in diabetic and non-diabetic patients and controlled for several confounders, including demographic factors, cardiovascular risk factors, disability and comorbidity. Diabetes was prevalent in 11.9% of our sample and depression in 15.4% of the subjects with diabetes, a finding which is highly comparable to the recent estimates of 11.4% [13] and 17.9% for type 2 diabetes [39]. As the mean age of subjects with diabetes in our sample was greater than 73 years of age, we expect that virtually all of them have type 2 diabetes. For example, in the Pathways Study [40], as many as 96% of the diabetes patients had type 2 diabetes at a mean age of 58 years.

Diabetes was associated with an increased risk of prevalent depression of 1.41 (95% CI: 1.08–1.83) after controlling for covariates, a finding that is similar to previous reports [13, 14]. Our study also revealed that diabetes was prospectively associated with an increased risk of incident depression at 2- and 5-year follow-up of 1.40 (95% CI: 1.03–1.90). This association was somewhat reduced after controlling for potential confounders and was no longer statistically significant (1.26; 95% CI: 0.90–1.77).

Table 3 Risks of prevalent and incident depression for subjects with diabetes stratified for presence of other chronic somatic disease, basic disability and instrumental disability

	Prevalent depression ^a	Incident depression ^a
No other chronic somatic disease	1.78 (1.16–2.72)	0.95 (0.54–1.70)
Other chronic somatic disease	1.26 (0.91–1.75)	1.47 (0.97–2.25)
No basic disability	1.53 (1.12–2.08)	1.25 (0.87–1.81)
Basic disability	1.05 (0.64–1.72)	1.39 (0.57–3.41)
No instrumental disability	1.46 (1.10–1.94)	1.33 (0.95–1.87)
Instrumental disability	1.26 (0.63–2.52)	0.57 (0.06–5.79)

Values are risk (95% CI)

^aControlling for age, sex, partner, education, hypertension, smoking, statin use and cognitive functioning

We explored the suggestion that disability and comorbidity play a role in this process and tested to what extent functional and instrumental disability and the presence of other chronic somatic diseases confounded and/or moderated the relationship between diabetes and depression. Adding these variables to our prediction models did not essentially change the effects of diabetes, so we conclude that the association is not confounded. Our findings do, however, suggest that disability and comorbidity moderate the association between diabetes and (prevalent and incident) depression. Thus we found an association between diabetes and prevalent depression only in the absence of comorbidity and disability. This finding is in line with a recent report [41] describing that in a sample of diabetic patients the risk of being depressed increased with the number of comorbid medical conditions: while one additional chronic disease was associated with 1.31 odds, three or more chronic diseases led to a 4.09-fold increased risk. Elsewhere, increased prevalence rates of depressive symptoms were also found only in the presence of comorbid medical conditions [14]. These findings suggest that the coexistence of multiple comorbid conditions and the related disabilities may largely account for the increased risk of depression in diabetes patients. Our study adds logically to this information and suggests that in patients with other chronic somatic diseases, diabetes does not further increase the risk of prevalent depression. On the other hand, in the absence of comorbidity, diabetes as such is associated with an increased risk of depression. However, since the interaction terms of diabetes with comorbidity were not statistically significant, these findings should be considered preliminary.

Since our study was the first to use a prospective design, we were also able to study whether the association of diabetes with incident depression is modified by chronic illness and disability. We did not find a clear pattern, as none of the subgroups was found to have a significant association between diabetes and incident depression. Still, in the subgroup of subjects with other chronic somatic diseases, we did find a non-significant trend for an association between diabetes and depression (OR 1.47 95% CI 0.97–2.25) ($P=0.07$). In contrast to the association with prevalent depression, the association with incident depression does not contain the potential bias of reverse

effects (i.e. of depression on diabetes). Interestingly, this finding suggests that it is especially in the presence of somatic comorbidity that diabetes leads to an additional risk of depression, thereby differing from our findings on prevalent depression.

Our findings should be considered in the light of the following strengths and weaknesses in the study design. A first strength is that our study used a large, representative community-based sample of subjects. Second, we used a reliable assessment of depression using a psychiatric interview rather than relying on self-reported data. Third, we controlled for a series of important confounders, including not only demographic variables, but also cardiovascular risk factors, disability and comorbidity. Among the weaknesses of our study is the fact that self-reported data on the presence of diabetes are potentially problematic, although, in fact, the use of self-reported data is common practice in this field of research. To eliminate possible errors, we also asked the respondents who the diagnosis was made by and what treatment they were offered, which gave us the possibility of conducting validation checks. In a recent report, moreover, a concordance rate of 96.3% was found between self-reported presence of diabetes and presence of diabetes as indicated by the treating physician [42]. However, many people or their physicians may be unaware of the presence of type 2 diabetes [43]. Our results therefore apply only to patients with detected diabetes and should be confirmed in a sample of subjects using an objective screening method for diabetes. A second limitation is the fact that depression was assessed at two intervals of 2 and 3 years. In the interim, an unknown number of subjects may have experienced both remittance and relapse. This may have influenced our results and led to an underestimation of incident episodes of depression. However, several studies [44] have concluded that the majority of late-life depressions follow a chronic course. Therefore, we believe this does not bias our results in an important way.

Many studies have reported a (cross-sectional) association between depression and (pre-)diabetes, but the direction of the relationship is not well understood [e.g. 10]. Most attention has been directed to the possibility that depression may lead to diabetes [45, 46]. We demonstrated that the reverse may also be true.

An increased prevalence of depression is found in several medical conditions. In recent years, several explanations for this relationship have been put forward, with either biological mechanisms (e.g. the hypothalamic–pituitary axis, platelet reactivity) or unhealthy life styles (e.g. smoking, non-compliance, lack of physical exercise) as underlying causes [47]. Two groups of hypotheses explaining the occurrence (or recurrence) of depressive symptoms have been identified [46]. According to the first, depression

results from biochemical changes directly due to the illness or its treatment. The other group postulates that depression results from the psychosocial demands or psychological factors related to the illness or its treatment. Our data do not enable us to support either of these hypotheses. We did, however, find that the association between diabetes and prevalent depression was largely independent of disability and comorbidity and that the association with incident depression seemed to be present only in subjects with other chronic somatic diseases.

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