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Title: Diabetes mellitus and risk of subsequent depression: A longitudinal study

Article Type: Research Paper

Keywords: depression; diabetes mellitus; incidence; longitudinal studies.

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Abstract: Background: Findings of previous studies on the association between diabetes and the risk of depression are contradictory. Furthermore, much less is known concerning the association among young adults.
Objective: To investigate whether diabetes is associated with an increased risk of subsequent development of depression, with emphasis on age-specific variations.
Design: A cohort study.
Setting: Claims data of one million subjects randomly selected from 23 million people covered by the Taiwan National Health Insurance program.
Participants: From the claims data, we identified 14,048 patients aged ≥ 20 years with newly diagnosed diabetes in 2000~2002 and randomly selected 55,608 non-diabetic subjects for comparison, that were frequency-matched by calendar year, age, and gender. Incidence rates of depression to the end of 2007 were identified, and risks were compared between the two groups.
Results: The incidence of depression was 1.80-times higher in the diabetic group than in nondiabetic subjects over a median follow-up of 6.5 years (adjusted hazard ratio [HR] = 1.46, 95% confidence interval [CI]: 1.24~1.71). Age-specific HRs for incidence of depression in relation to diabetes were not statistically different between the patient subgroups aged 20-39, 40-49, 50-59, 60-69 and ≥ 70 years (p value for age-diabetes interaction=0.33). Stratified analyses showed that the association was much stronger for subjects without comorbid cardiovascular disease than for those with this comorbidity. Insulin treatment was associated with a 43% reduced risk of depression in diabetic patients.
Conclusions: In this population-based study, diabetic patients were at a higher risk for subsequent depression. Adequate treatment reduced the risk.

Response to Reviewers: EDITORIAL COMMENTS

Thank you for your comprehensive response to the reviewers comments and further analysis and interpretation of the data from your study. There are still some aspects of the data analysis and presentation of the results that are unclear to the reader and would benefit from further clarification.

Reviewer #4: Review for IJNS10-00676R2
I am not satisfied with how the authors have described the null interaction term with age in the text - in the response they state that they tested that there was NO SIGNIFICANT INTERACTION between age

and diabetes status, and yet in the text there is NO MENTION of this null result, and instead they continue to describe the findings as though there is a diminishing effect with age (the interaction term says this is not true). The statements "In unadjusted and partially adjusted models the association between diabetes and risk of depression DECREASED slightly with aging." and "test for age-diabetes interaction, 0.33") are INCOMPATIBLE. Only the latter statement is correct - there is NO EVIDENCE THAT THE RELATIONSHIP between depression and diabetes varies with age.
The authors need to state explicitly in the METHODS that they test for the diabetes-age interaction. The abstract, results & discussion need to be re-written to properly state what they actually found (that is, no effect of age) and eliminate statement such as "decreased slightly", "diminished with age", "more pronounced" - these are not true statements according to the interaction term.

Reply:
Thank you for your suggestions. We have withdrawn all statements with regard to differences in diabetes-depression association among age groups in this revision and re-written the relevant descriptions. The statistical methods used to test for interaction effect are also described in the "methods" section.

In ABSTRACT:
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The age-specific risk of depression decreased slightly with aging, as the significance diminished for those aged ≥ 70 years.
Added-
Age-specific HRs for incidence of depression in relation to diabetes were not statistically different between the patient subgroups aged 20-39, 40-49, 50-59, 60-69 and ≥ 70 years (p value for age-diabetes interaction=0.33). (please see page 1, the last 2 lines, and page 2, line 1, in the revision).

In "What this paper adds" box:
Deleted-
The risk of depression associated with diabetes diminishes in patients ages ≥ 70 years.
Added-
Diabetes was associated with increased risk of subsequent depression, and the association did not vary by age. (please see page 3 in the revision)

In METHODS:
Deleted-
We also performed regression analyses among patient subgroups of CVD to assess whether there was an effect of an interaction between comorbid CVD and diabetes.
Added-
To assess interaction effect between age and diabetes, we performed the likelihood ratio test comparing models with and without interaction terms between the 5 age groups and diabetes. The interaction effect between comorbid CVD and diabetes was also examined. (please see page 9, lines 4-7 from the last line)

In RESULTS:
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The age-stratified analysis showed that among all age groups of < 70 years, diabetes was significantly associated with a greater risk of developing depression. In the unadjusted and partially adjusted models, the association between diabetes and risk of depression decreased slightly with aging, from an HR of 1.98 for the 20~29-year group to 1.84 for the 60~69-year group and 1.23 for the oldest group (model 1; test for age-diabetes interaction, p=0.33). In the model further adjusted for cardiovascular comorbidity, the HR became statistically insignificantly in patients aged 20~39 years. We found no

statistically significant association between diabetes and subsequent depression among subjects ≥ 70 years old in any model.
Added-
We found no significant interaction between age and diabetes on the risk of subsequent depression (likelihood ratio test for age-diabetes interaction in model 2, p=0.33), which indicated the estimated HRs for the diabetes-depression association were not significantly different between age groups. (please see age 11, lines 2-5, in the revision)
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Diabetic subjects aged 20~39 and 40~49 years had respective HRs of 1.93 (95% CI: 1.10~3.40) and 1.85 (95% CI: 1.16~2.95), and the risk was weaker for those aged ≥ 70 years (HR: 1.58, 95% CI: 0.36~6.94).
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The corresponding figures for patients aged 20~39, 40~49 and ≥ 70 years were 1.93 (95% CI: 1.10~3.40), 1.85 (95% CI: 1.16~2.95), and 1.58 (95% CI: 0.36~6.94), respectively. But the differences in these five age-specific HRs were not statistically significant (The p-value for age-diabetes interaction, 0.48). (please see page 11, paragraph 2, last 4 lines)

In DISCUSSION:
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The association was more pronounced in persons who were aged < 70 years
and those without comorbid CVD.
Added-
No significant age-specific variation was observed in the association. (please see page 12, paragraph 2, the last 2 lines)
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This study revealed an appreciably increased risk of developing depression associated with diabetes, particularly for younger patients. People in this age group with diabetes could most effectively benefit from screening for depression, as they are at higher risk and have long-term economic and social burdens due to concurrent diabetes and depression.
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This study revealed an appreciably increased risk of developing depression associated with diabetes, and the association did not vary by age. (please see page 16, lines 3-4)

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Part 2 identifies recognized guidelines for scientific reporting, which you should use to prepare your manuscript *(required for systematic reviews and original research)*

Part 3 Is a self assessment checklist that is designed to help to ensure that your research or review manuscript meets basic standards and the journal's Guide for Authors. *(optional only)*

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Word count	258 in the abstract; 2483 in the text	
Was ethical approval given and by whom? (give any reference number)	This study used claims data containing scrambled personal identifications. Institutional review board approval was exempted for conducting this study.	
Please state any conflicts of interest	None.	
Please state sources of funding and the role of funders in the conduct of the research	This study was supported partly by the National Science Council, Executive Yuan, Taiwan, Republic of China (NSC 97-2625-M-039-003), China Medical University Hospital (grant number 1MS1) and Taiwan Department of Health Clinical Trial and Research Center for Excellence (DOH99-TD-B-111-004) and Cancer Research Center of Excellence (DOH99-TD-C-111-005). The funding sources had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.	
Please state any study registry number (e.g. ISRCTN)	Not applicable.	
Title	The title is in the format 'Topic / question: design/type of paper' and identifies the population / care setting studied. *(e.g. The effectiveness of telephone support for adolescents with insulin dependant diabetes: controlled before and after study: the structure is optional for* discussion papers, editorials and commentaries*)*	X
Abstract	A structured abstract appropriate to the design (see *guidelines for authors)*. Reports of controlled trials should follow the CONSORT format (does not apply to editorials or commentaries, Abstracts for discussion papers need not be structured)	X
Key words	Between four and six key words have been provided in alphabetical order, which accurately identify the paper's subject, purpose, method and focus. Use the Medical Subject Headings (MeSH®) thesaurus or Cumulative Index to Nursing and Allied Health (CINAHL) headings where possible (see http://www.nlm.nih.gov/mesh/meshhome.html).	X
What the paper adds	Bullet points have been included that identify existing research knowledge relating to the specific research question / topic (what is already known) and a summary of the new knowledge added by this study *(see Guide for Authors*, does not apply to editorials or commentaries)	X
References	Citations accord to the journal's format (Author, date) and reference list includes full details of all cited references in the proper format and alphabetical order (see *Guide for Authors)*	X
Other Published accounts	*All* published and in press accounts of the study from which data in this paper originate are referred to in the paper and the relationship between this and other publications from the same study is made clear (see *Guide for Authors*)	X

	The study is referred to by a distinctive name which will be used in any future publications to identify that it as the same study.	
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Systematic Review of Controlled Trials	PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses http://www.equator-network.org/index.aspx?o=1032		
Systematic Review of Observational Studies	MOOSE Meta-analysis of Observational Studies in Epidemiology http://www.equator-network.org/index.aspx?o=1032		
	Qualitative researchers might wish to consult the guideline listed below		
Qualitative studies	COREQ: Consolidated criteria for reporting qualitative research Tong, A., Sainsbury, P., Craig, J., 2007. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care* 19 (6), 349-357. (http://dx.doi.org/10.1093/intqhc/mzm042)		
Other (please give source)			
Not applicable (please elaborate)			

Pei-Chun Chen, PhD
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September 12, 2011

Sharon McKinley, PhD
Editor
International Journal of Nursing Studies

Ms. Ref. No.: IJNS-D-10-00676 (Revision 3)
Title: Diabetes mellitus and risk of subsequent depression: a longitudinal study

Dear Prof. McKinley:

Thank you very much for your letter of September 8, 2011 and the reviewer's comments for the above referred manuscript. We have revised the manuscript and responded to all comments point-by-point. All additions to the manuscript have been put in bold blue. All deletions of the text also have been indicated in the "response to reviewer" document.

All authors have agreed to this submission and no similar paper has been submitted for publication elsewhere. There is no interest confliction involved for this submission.

Thank you again for your review of this revision and consideration for publication in the journal.

Sincerely,

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Assistant Professor
Tel: 886-4-2205-3366 ext 6119
Fax: 886-4-2201-9901
e-mail: peichun@mail.cmu.edu.tw

Response to reviewers

Ms. Ref. No.: IJNS-D-10-00676 (Revision 3)
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***Title Page (with author details and affiliations)**

Ms. Ref. No.: IJNS-D-10-00676 (Revision 3)

Title: Diabetes mellitus and risk of subsequent depression: A longitudinal study

Yi-Min Hsu[a], Li-Ting Su[b,c,d], Hui-Mei Chang[a], Fung-Chang Sung[c], Shu-Yu Lyu[e], and Pei-Chun Chen[b,f,g]

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Running head: Diabetes and depression risk

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Sources of funding:
This study was supported partly by the National Science Council, Executive Yuan, Taiwan, Republic of China (NSC 97-2625-M-039-003), China Medical University Hospital (grant number 1MS1) and Taiwan Department of Health Clinical Trial and Research Center for Excellence (DOH100-TD-B-111-004) and Cancer Research Center of Excellence (DOH100-TD-C-111-005). The funding sources had no involvement in study design, data collection, analysis and interpretation of data, writing of the report, and the decision to submit the paper for publication.

Conflict of Interest: None declared.

Ms. Ref. No.: IJNS-D-10-00676 (Revision 3)

Title Diabetes mellitus and the risk of subsequent depression: a longitudinal study

Abstract

Background: Findings of previous studies on the association between diabetes and the risk of depression are contradictory. Furthermore, much less is known concerning the association among young adults.

Objective: To investigate whether diabetes is associated with an increased risk of subsequent development of depression, with emphasis on age-specific variations.

Design: A cohort study.

Setting: Claims data of one million subjects randomly selected from 23 million people covered by the Taiwan National Health Insurance program.

Participants: From the claims data, we identified 14,048 patients aged ≥ 20 years with newly diagnosed diabetes in 2000~2002 and randomly selected 55,608 non-diabetic subjects for comparison, that were frequency-matched by calendar year, age, and gender. Incidence rates of depression to the end of 2007 were identified, and risks were compared between the two groups.

Results: The incidence of depression was 1.80-times higher in the diabetic group than in nondiabetic subjects over a median follow-up of 6.5 years (adjusted hazard ratio [HR] = 1.46, 95% confidence interval [CI]: 1.24~1.71). **Age-specific HRs for incidence of depression in relation to diabetes were not statistically different between the patient subgroups aged**

20-39, 40-49, 50-59, 60-69 and ≥ 70 years (p value for age-diabetes interaction=0.33).

Stratified analyses showed that the association was much stronger for subjects without comorbid cardiovascular disease than for those with this comorbidity. Insulin treatment was associated with a 43% reduced risk of depression in diabetic patients.

Conclusions: In this population-based study, diabetic patients were at a higher risk for subsequent depression. Adequate treatment reduced the risk.

Keywords: depression; diabetes mellitus; incidence; longitudinal studies.

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What is already known about the topic?

• Studies have demonstrated an association between depression and diabetes.

• Whether the incidence of depression is subsequently elevated among patients diagnosed with diabetes is controversial.

• The effect of diabetes on subsequent depression may differ with age.

What this paper adds?

• Diabetes was associated with increased risk of subsequent depression, and the association did not vary by age.

• The association between diabetes and an elevated risk of developing depression was stronger in patients without cardiovascular disease than in those with the disease.

1. Introduction

Diabetes is an increasingly prevalent chronic disease often comorbid with medical conditions that lead to health and economic burdens (Wild et al., 2004; Campbell and Martin, 2009). It is recognized that patients with type 2 diabetes have a higher prevalence of depression compared to nondiabetic subjects (Aliet al., 2006; Anderson et al., 2001). Several prospective studies examined the bidirectional temporal association between the two diseases, indicating an excess risk of diabetes incidence in subjects with depression (Golden et al., 2008; Mezuk et al., 2008). However, whether the incidence of depression is subsequently elevated among patients diagnosed with diabetes is controversial.

A meta-analysis study examined this issue and suggested that the association may differ with age (Mezuk et al., 2008). Most previous studies assessed the relationship between diabetes and the incidence of depression in middle-aged and older populations (de Jonge et al., 2006; Kim et al., 2006; Maraldi et al., 2007; Palinkas et al., 2004; Polsky et al., 2005). Little information is available on the risk for young adults compared to older groups. A cross-sectional study reported that the association between diabetes and the prevalence of depression was stronger in patients younger than 40 years old than in older patients (Zhao et al., 2006), but data on the incidences are not available. Given the increasing prevalence of the onset of diabetes in young adults (Lee et al., 2007), it is important to public health to investigate the risk among patients of an earlier age with diabetes. The economic and social

burdens could be particularly important for young patients, as they have longer life spans, and the presence of depression deteriorates the quality of life of patients with diabetes (Eren et al., 2008).

Using a nationwide database from the National Health Insurance (NHI) program in Taiwan, we conducted a population-based retrospective cohort study to examine the association between diabetes and the risk of subsequent depression, emphasizing age-specific variations. We also assessed whether cardiovascular disease (CVD), which usually coexists with diabetes, modifies the association between diabetes and depression. This knowledge could provide recommendations for primary care practice on identifying targets of prevention efforts.

2. Methods

2.1. Data Source

Taiwan's NHI, a government-operated, single-payer health insurance program reformed in 1995, covered approximately 99% of the total 23 million people in Taiwan by 2007 (Lu and Hsiao, 2003; NHI profile, 2009). For research and administrative purposes, the National Health Research Institute maintains computerized claims data, which include files of ambulatory care, inpatient care, prescription drugs, and a registry of beneficiaries, and releases the database for public access. This study used a subset consisting of longitudinal claims data for 1 million subjects randomly selected from all beneficiaries covered by the

NHI. Using this dataset, we were able to select study subjects and obtain longitudinal healthcare information for each subject. In order to protect patients' privacy, all patient-level information can be retrieved and linked only through scrambled personal identification, and thus, this study was exempt from institutional review board approval.

2.2. Patient Population and Subjects in the Comparison Cohort

We defined diabetes mellitus (DM) using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) code 250. Patients with diabetes included in this study were individuals aged 20 years and above, newly diagnosed in 2000~2002 identified from ambulatory care visits or admission records. Subjects with a prior diabetes history were excluded. In an attempt to reduce the misclassification of the diabetes status, we included only patients who received medical care at least three times for diabetes during the 3-year period.

A comparison cohort was randomly selected from individuals with no history of diabetes. For each patient with diabetes, four persons free of diabetes were randomly selected for the comparison cohort which were frequency matched with distributions of the year of diagnosis, age (at 10-year intervals), and gender. The date of entering this study for both patients with diabetes and subjects in the comparison cohort was the date when the person was identified by the attending physician. We excluded persons with a history of depression at the baseline, leaving 14,048 patients with diabetes and 55,608 subjects in the comparison

cohort for the data analysis. A patient was defined as having a depression history if he or she had at least one outpatient and/or inpatient claim for depression from 1996, when the computerized claims data were available, until the date of entering this study.

2.3. Measures of Study Outcomes and Comorbid Conditions

Study subjects were followed up to the end of 2007 to measure the incidence of depression. We identified subjects as having developed depression if they had at least two treatment claims for depression in outpatient visits and/or hospitalizations for ICD-9-CM code 296.2 or 296.3 during the follow-up period. There were three diagnosis fields on each outpatient claim and five diagnosis fields for inpatient claims. Follow-up person-years were determined by calculating the time interval between the entry date and the earliest of one of the following: a diagnosis of depression, the date of withdrawal from the NHI program including loss to follow-up or death, or December 31, 2007.

In the data analyses, we took into account several health conditions that are reported to be associated with diabetes and depression (Brown et al., 2006). These medical histories included hypertension (ICD-9-CM codes 401-405), hyperlipidemia (ICD-9-CM code 272), coronary artery disease (CAD; ICD-9-CM codes 410-414, 425-429), stroke (ICD-9-CM codes 430-438), dementia (ICD-9-CM codes 290.0, 290.1, 290.2, 290.3, and 331.0), Parkinson's disease (ICD-9-CM code 332), and cancer (ICD-9-CM codes 140-209). We considered these medical conditions to be present if the corresponding diagnosis was listed on outpatient visits

claims and/or hospitalizations records of study subjects prior the date of their entering this study. In the data analysis, we defined CVD as at least one diagnosis of hypertension, hyperlipidemia, CAD, and/or stroke present before the date of entering the study. We also identified insulin use among patients with diabetes, as previous studies reported an association between insulin use and the incidence of depression (Ali et al., 2006; Brown et al., 2006).

2.4. Statistical Analysis

We compared differences in sociodemographic characteristics including age, gender, occupation, level of urbanization of residential area, and monthly income, and comorbidities between patients with diabetes and the nondiabetic comparison group. Levels of urbanization were determined by the population density (persons/km^2) in the region where the study subject was registered for insurance. Areas in the lowest and highest quartiles of population density were classified as areas of low and high urbanization, respectively; those in the other two quartiles were categorized as moderately urbanized areas.

The Kaplan-Meier method was used to compare the cumulative incidence of depression in the diabetes and comparison groups, and a log-rank test was used to examine the significance level of differences between groups. We used Cox proportion hazard regression analyses to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of depression for patients with diabetes using the comparison group as the reference group. To assess the effect

of diabetes in young patients, we performed all regression analysis by stratifying subjects into five age groups (20~39, 40~49, 50~59, 60~69, and ≥ 70 years) based on the age at entry into the study. We combined patients aged 20~29 and 30~39 years to avoid imprecise estimates due to the small numbers of subjects in these two age groups. A univariate analysis estimated the crude association with diabetes. The multivariable-adjusted models included age, gender, occupation, income, and medical history, such as hypertension, hyperlipidemia, CAD, and stroke. We pre-selected several potential confounding factors based on knowledge from a literature review and then used several approaches to select variables for inclusion in the models for adjustment. We examined whether these variables were substantially associated with diabetes and depression in descriptive analyses. The crude and adjusted associations were also compared to evaluate whether the covariates influenced the strength of the association between diabetes and the incidence of depression. **To assess interaction effect between age and diabetes, we performed the likelihood ratio test comparing models with and without interaction terms between the 5 age groups and the diabetes. The interaction effect between comorbid CVD and diabetes was also examined.** In addition, regression analyses were repeated for patients with diabetes stratified by indication of insulin use. The proportional hazard assumption underlying the Cox regression models was examined using a test of scaled Schoenfeld residuals and time-dependent covariates. All analyses were

performed using SAS statistical software (vers. 9.1 for Windows; SAS Institute, Cary, NC), and all statistical tests were two-sided.

3. Results

Compared to subjects in the comparison cohort, patients with diabetes were less likely to be white collar workers and had lower incomes (Table 1). Patients in the diabetes group were much more likely to have hypertension (49.0% vs. 22.3%, $p<0.001$), hyperlipidemia (29.7% vs. 5.2%, $p<0.001$), CAD (27.8% vs. 14.8%, $p<0.001$), and stroke (12.1% vs. 6.4%, $p<0.001$).

The Kaplan-Meier analysis showed that the cumulative probability of depression incidence was higher for patients with diabetes than for those without diabetes during the study period ($p<0.001$, Figure 1). The cumulative incidence of depression was higher in diabetic patients than in nondiabetic subjects in all age groups (Figure 2). The difference in the incidences between each age group pair declined with increasing age, and was not significant only for the subgroup aged ≥ 70 years.

With a median follow-up of 6.5 years in both groups, the overall incidence of depression was 1.80-times higher in the diabetic group than in the comparison group (28.5 vs. 15.9 per 10,000 person-years) (Table 2). Relative to the non-diabetic comparison group, patients with diabetes had an HR of 1.77 for developing depression (95% CI: 1.53~2.06, model 1) after controlling for age, gender, and sociodemographic characteristics. The HR was

slightly attenuated to 1.46 (95% CI: 1.24~1.71, model 2) after further adjusting for the medical history. **We found no significant interaction between age and diabetes on the risk of subsequent depression (likelihood ratio test for age-diabetes interaction in model 2, *p*=0.33), which indicated the estimated HRs for the diabetes-depression association were not significantly different between age groups.**

Table 3 presents the adjusted age-specific HR for the risk of depression in relation to diabetes for patients with and without CVD. We found a statistically significant effect of an interaction between CVDs and diabetes ($p<0.001$). Diabetes was associated with an appreciably increased risk of depression in patients without CVDs (HR: 2.21, 95% CI: 1.70~2.86) but not in those with the disease. Among diabetes patients without CVD, those aged 60~69 years had the greatest HR (3.82, 95% CI: 2.07~7.07), followed by the 50~59-year group (HR: 2.24, 95% CI: =1.33~3.75). **The corresponding figures for patients aged 20~39, 40~49 and ≥ 70 years were 1.93 (95% CI: 1.10~3.40), 1.85 (95% CI: 1.16~2.95), and 1.58 (95% CI: 0.36~6.94), respectively. But the differences in these five age-specific HRs were not statistically significant (The p-value for age-diabetes interaction, 0.48).**

Table 4 shows that diabetes patients with insulin treatment were less likely to have a risk of subsequent depression. The beneficial effect was the greatest for diabetic patients with comorbid CVD, with an HR of 0.57 (95% CI: 0.38~0.86) relative to comparison subjects. Diabetic patients who did not use insulin were at a much greater risk of experiencing

depression than those prescribed with insulin. Further analyses of other antidiabetes drugs, including biguanide, sulfonylurea, thiazolidinedione, and alpha-glucosidase inhibitors, revealed similar findings (data not shown).

4. Discussion

In this population-based retrospective cohort study in Taiwan, newly diagnosed diabetes was associated with an increased incidence of depression over a median follow-up of 6.5 years. The association was more pronounced in persons without comorbid CVD. **No significant age-specific variation was observed in the association.**

Previous studies from Western populations reported a marginal or no association between diabetes and the incidence of depression (Brown et al., 2006; Engum, 2007; Palinkas et al., 2004; Polsky et al., 2005). Differences in methodology and inclusion of study subjects between those studies and ours may explain the inconsistent findings. First, previous studies assessed diabetes using self-reported data, blood tests for fasting glucose, or claims data that may have included patients with different severities of diabetes, thereby yielding inconsistent findings. (Brown et al., 2006; Engum, 2007; Mezuk et al., 2008; Polsky et al., 2005). Second, most previous studies were limited to Western populations (Brown et al., 2006; Engum, 2007); few data are available for Asian populations. Ethnic differences in the risk of having depression may exist among patients with diabetes (Ali et al., 2009). Kim et al. (2006) observed no elevated risk associated with diabetes in Koreans aged ≥ 65 years, which is in

line with our observations for the older age group. The Multi-Ethnic Study of Atherosclerosis included Chinese-Americans in their analysis, but the authors did not report the strength of ethnicity-specific associations (Golden et al., 2008).

Some possible mechanisms may explain the association between diabetes and the incidence of depression. Complications of diabetes and psychological pressure resulting from coping with diabetes may induce subsequent depression (Golden et al., 2008; Talbot and Nouwen, 2000). de Jonge et al. (2006) found that diabetes was associated with an increased prevalence of depression only in subjects without comorbidity, but the incidence of depression was more likely to be pronounced in those with the presence of a comorbidity. In the present study, diabetes did not add an appreciably risk to depression in subjects with preexisting CVD. A possible explanation for this observation is that we included subjects with new-onset diabetes. They had not yet developed serious complications. The impact may be more pronounced in patients with diabetes for a longer duration. It is important to note that insulin treatment has a protective effect in patients with the comorbidity of CVD by reducing the risk of depression by 43%. We also found a similar beneficial effect from taking other antidiabetic medicines (data not shown). This finding indicates the importance of adherence to medical treatment recommendations for patients with diabetes.

We also found in this study that among all age groups, the incidence of depression in the comparison group was highest for patients aged $\geq$ 70 years, but that in the diabetic group

was the lowest for this age group. This discrepancy yielded a smaller HR for developing depression in these old diabetic patients. Other risk factors may be more prominent than diabetes in the association with depression for older patients.

The following limitations merit consideration before concluding this study. First, relying on administrative data of the diagnosis may include some extent of misclassification of diseases. In an attempt to reduce the likelihood of misclassification, we used at least two consecutively identical diagnoses to define diabetes and depression. In addition, we were able to capture disease events at any time point when a subject had a medical care visit, which reduced the likelihood of underestimating incident events that occurred during the interval between follow-up visits (de Jonge et al., 2006). Second, we were unable to include patients with mild symptoms who were less likely to seek health care, and patients who had not reported their mood symptoms. Our study results thus apply to patients with detected and treated diabetes and depression. Previous studies reported that the prevalence of depression is lower in South Asians than in white Europeans, suggesting a possibility of culture differences in the presentation of depression (Ali et al., 2009; Ineichen, 1990; Yeung et al., 2004). Asians may have greater difficulty or may be more reluctant to express depressive symptoms because of the stigma associated with mental disorders, which could lead to a lower sensitivity of the diagnosis of depression. Thus, in this study, the incidence of depression may have been underestimated. However, the underreporting associated with cultural factors would be of

similar magnitudes in both the diabetes and comparison groups and thus would likely have little effect on the estimated relative risk (hazard ratio). Third, we did not differentiate type 1 from type 2 diabetes in the claims data. The relationship with depression might differ between these two types of diabetes, as the pathophysiology of these conditions differs. In this study, most patients were type 2 diabetes because 97% of patients with diabetes have type 2 diabetes in Taiwan (Chuang et al., 2001). Fourth, some potential confounding factors for the association between diabetes and depression, such as the body-mass index and smoking status, are not included in the NHI database. Residual confounding might have occurred in the observed association. Fifth, because the computerized claims data were unavailable before 1996, we were unable to identify depression diagnosed earlier. Thus, we could not exclude the possibility of including recurrent cases of depression, particularly among older subjects. Last, the small number of subjects in the stratified analyses of age groups, CVD, and diabetes may have caused imprecise estimates and insufficient statistical power to detect a moderate association.

Findings of this study have important implications for nursing and clinical practice. Evidence has shown that among patients with both diabetes and depression, those who receive depression treatment are at a lower risk of mortality than those without an intervention (Bogner et al., 2007). Depression is an important predictor of suicide, and the risk of suicide increases when depressive symptoms occur and become severe. Thus, it is crucial to develop

intervention strategies to help patients cope with psychological pressure in the early stage when caring for patients with diabetes.

This study revealed an appreciably increased risk of developing depression associated with diabetes, **and the association did not vary by age.** Further investigation of the role of CVD in the association between diabetes and depression is warranted. In addition, insulin and antidiabetic medications may be associated with a reduced risk of depression. Further studies designed to assess treatment effects are needed to clarify this issue.

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Figure Legends

Figure 1. Kaplan-Meier curves of the time to occurrence of depression for patients with diabetes and the comparison group.

Figure 2. Kaplan-Meier curves of the time to occurrence of depression for patients with diabetes and the comparison group by age.

Figure1

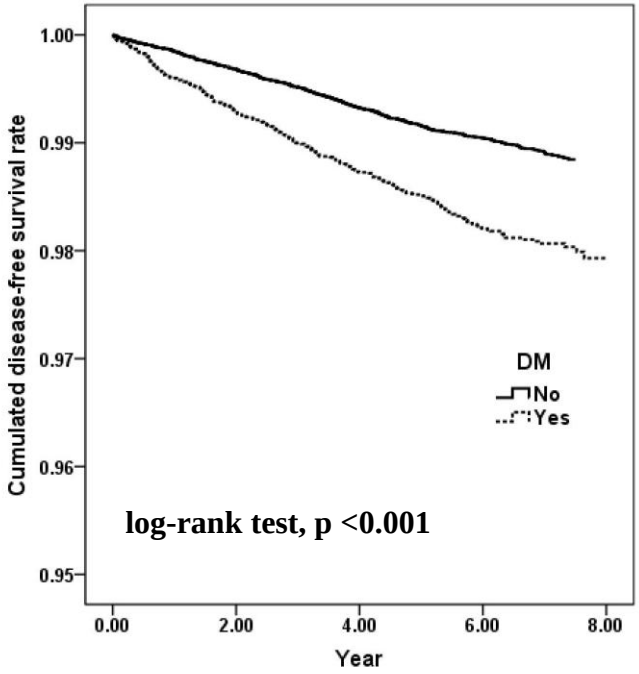
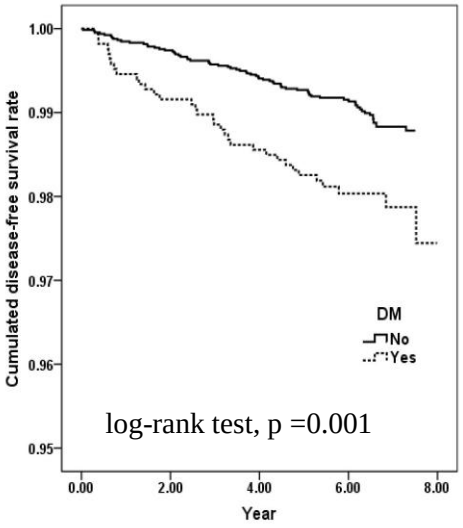
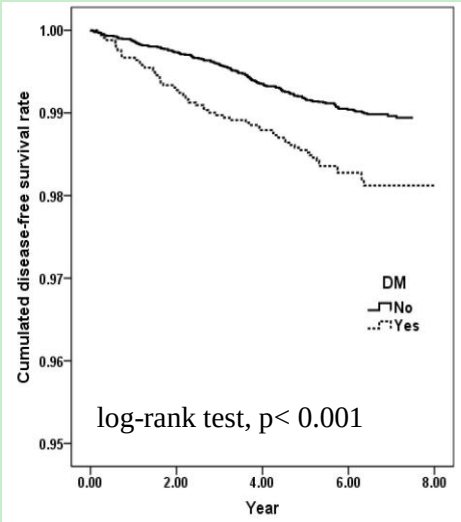

1.00
0.99
0.98
0.97
0.96
0.95
Cumulated disease-free survival rate
DM
No
Yes
log-rank test, p <0.001
0.00
2.00
4.00
6.00
8.00
Year

Figure2

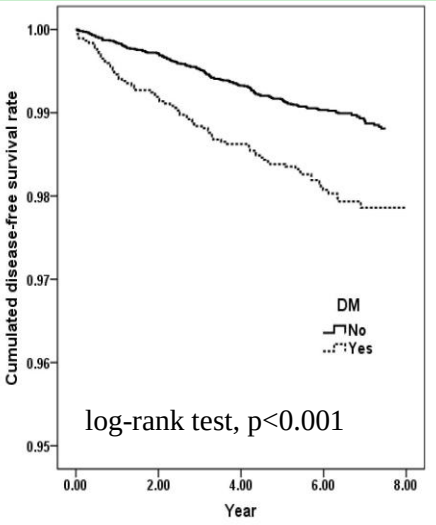
20-39 years



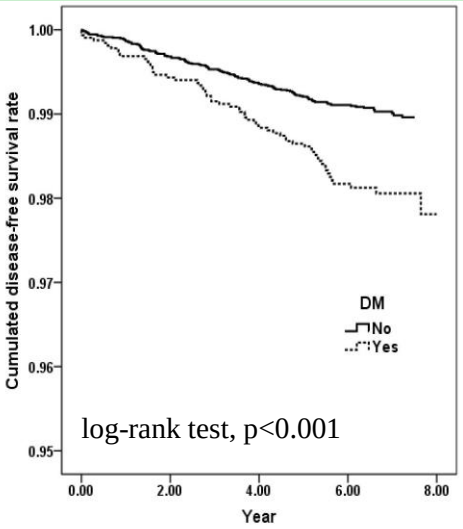
40-49 years



50-59 years



60-69 years



≥ 70 years

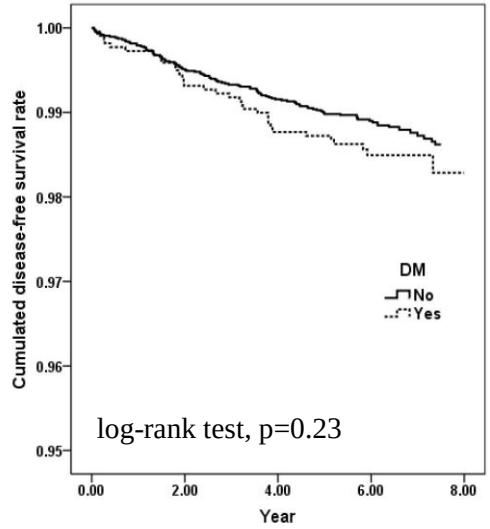


Table 1
Socio-demographic characteristics and comorbidity in patients with diabetes and in comparison cohort

	Comparison group (n=55,608)	Pubjects with diabetes (n=14,048)	*p*-value
Women, n (%)	26782 (48.2)	6808 (48.5)	0.52
Age, years, n (%)			1.00
20-39	6567 (11.8)	1662 (11.8)	
40-49	13128 (23.6)	3310 (23.6)	
50-59	14692 (26.4)	3707 (26.4)	
60-69	12589 (22.6)	3178 (22.6)	
≥70	8632 (15.5)	2191 (15.6)	
Mean (SD)	55.1 (13.5)	55.6 (13.1)	<0.001
Occupation, n (%)			<0.001
White collar	21504 (38.7)	5000 (35.6)	
Blue collar	22838 (41.1)	6069 (43.2)	
Others	11266 (20.3)	2979 (21.2)	
Urbanization, n (%)			0.95
Low	2356 (4.2)	587 (4.2)	
Moderate	17282 (31.1)	4363 (31.1)	
High	35969 (64.7)	9097 (64.8)	
Income, NTD, n (%)			<0.001
<15,000	23075 (41.5)	6210 (44.2)	
15,000-29,999	23657 (42.5)	5822 (41.4)	
≥30,000	8876 (16.0)	2016 (14.4)	
Comorbidity, n (%)			
Hypertension	12581 (22.6)	6876 (49.0)	<0.001
Hyperlipidemia	2945 (5.3)	4178 (29.7)	<0.001
Coronary artery disease	8380 (15.1)	3905 (27.8)	<0.001
Stroke	3621 (6.5)	17.2 (12.1)	<0.001
Dementia	244 (0.4)	98 (0.7)	<0.001
Parkinson's disease	511 (0.9)	199 (1.4)	<0.001
Cancer	896 (1.6)	267 (1.9)	0.017
Diabetes treatment, n (%)			
Insulin	-	3816 (27.2)	
Biguanide	-	9352 (66.6)	
Sulfonylurea	-	9270 (66.0)	
Thiazolidinedione	-	2390 (17.0)	
Alpha-glucosidase inhibitor	-	2400 (17.1)	

NTD=new Taiwan dollars.

Table 2

Age-specific incidence and hazard ratio of depression associated with diabetes

Age, years	Comparison group			Patients with diabetes			Hazard ratio (95% confidence interval)		
	n, depression	Person-years at risk	Incidence[a]	n, depression	Person-years at risk	Incidence[a]	Unadjusted	Model 1	Model 2
All	572	360870	15.9	258	90460	28.5	1.79 (1.54-2.07)	1.77 (1.53-2.06)	1.46 (1.24-1.71)
20-39	67	42425	15.8	34	10633	32.0	1.97 (1.30-2.99)	1.98 (1.30-3.03)	1.39 (0.84-2.30)
40-49	130	85661	15.2	59	21412	27.6	1.82 (1.34-2.48)	1.86 (1.36-2.54)	1.68 (1.18-2.39)
50-59	153	95117	16.1	73	23808	30.7	1.92 (1.45-2.53)	1.89 (1.43-2.50)	1.48 (1.08-2.01)
60-69	119	81970	14.5	59	20542	28.7	1.93 (1.41-2.65)	1.84 (1.35-2.53)	1.60 (1.15-2.25)
≥70	103	55697	18.5	33	14065	23.5	1.27 (0.86-1.89)	1.23 (0.83-1.83)	0.98 (0.65-1.47)

[a]per 10,000 person-years

Model 1 was adjusted for age, sex, occupation and income.

Model 2 was adjusted for variables in model 1 and comorbidiy including hypertension, stroke, hyperlipidemia and coronary artery disease.

Table 3
Adjusted age-specific incidence and hazard ratio of depression associated with diabetes by history of cardiovascular disease

Age, years	Patients with diabetes		Comparison group		Hazard ratio (95% CI) in relation to diabetes
	No. of depression	Incidence	No. of depression	incidence	
Patients with cardiovascular disease[a]					
20-39	17	3.7	14	6.4	0.69 (0.33-1.44)
40-49	37	3.1	32	2.6	1.18 (0.73-1.91)
50-59	55	3.4	80	2.9	1.19 (0.85-1.68)
60-69	44	2.7	81	2.2	1.18 (0.82-1.71)
≥70	31	2.5	88	2.5	0.99 (0.65-1.49)
All	184	3.0	295	2.6	1.10 (0.91-1.33)
Patients without cardiovascular disease[a]					
20-39	17	2.8	53	1.3	1.93 (1.10-3.40)
40-49	22	2.3	98	1.3	1.85 (1.16-2.95)
50-59	18	2.3	73	1.1	2.24 (1.33-3.75)
60-69	15	3.4	38	0.8	3.82 (2.07-7.07)
≥70	2	1.1	15	0.7	1.58 (0.36-6.94)
All	74	2.5	277	1.1	2.21 (1.70-2.86)

CI = confidence interval.
Models were adjusted for age, sex, occupation and income.
[a]Patients with cardiovascular disease were identified if they had been diagnosed with any one of the following medical conditions prior to the date of entering this study: hypertension, hyperlipidemia, coronary artery disease and stroke.

Table 4

Adjusted hazard ratio of depression associated with diabetes and insulin use by age and history of cardiovascular disease

	Age, years					
	All	20-39	40-49	50-59	60-69	≥70
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Patients with CVD[a]						
No diabetes	1.00	1.00	1.00	1.00	1.00	1.00
Diabetes with insulin use	0.57 (0.38-0.86)	0.20 (0.03-1.53)	0.56 (0.20-1.58)	0.83 (0.41-1.65)	0.66 (0.31-1.44)	0.37 (0.14-0.998)
Diabetes without insulin use	1.30 (1.06-1.58)	0.81 (0.39-1.69)	1.37 (0.84-2.23)	1.31 (0.91-1.88)	1.39 (0.94-2.05)	1.32 (0.85-2.03)
Patients without CVD[a]						
No diabetes	1.00	1.00	1.00	1.00	1.00	1.00
Diabetes with insulin use	1.85 (1.13-3.03)	1.94 (0.76-4.95)	1.35 (0.49-3.68)	2.83 (1.23-6.52)	1.61 (0.38-6.73)	- -
Diabetes without insulin use	2.34 (1.76-3.13)	1.93 (1.02-3.67)	2.01 (1.21-3.34)	2.02 (1.10-3.73)	4.84 (2.54-9.23)	2.86 (0.65-12.52)

HR=hazard ratio; CI=confidence interval.

Models were adjusted for age, sex, occupation and income.

[a]Patients with cardiovascular disease (CVD) were identified if they had been diagnosed with any one of the following medical conditions prior to the index date: hypertension, hyperlipidemia, coronary artery disease and stroke.