JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Longitudinal investigation of the reciprocal relationship between depressive symptoms and glycemic control: The moderation effects of sex and perceived support

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Keywords
Depression, Family support, Glycemic control

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J Diabetes Investig 2019; 10: 801–808

doi: 10.1111/jdi.12969

ABSTRACT

Aims/Introduction: The present study investigated the longitudinal associations between depressive symptoms and glycemic control in nationally representative adults with type 2 diabetes, and tested the effects of sex and perceived family support in moderating this association.

Materials and Methods: In this longitudinal study of middle-aged and older adults who participated in the 2002 and 2006 Health and Retirement Study, and the 2003 and 2006 Diabetes Study (n = 398), we applied a cross-lagged structural equation model to examine the reciprocal relationship between depressive symptoms and glycemic control over a 3-year period.

Results: Men and women were not different in terms of the depressive symptoms and glycemic control relationship, with a stronger association noted for higher depressive symptom scores predicting worse glycemic control (β = 0.22, critical ratio 3.03), as opposed to worse glycemic control predicting higher depressive symptom scores. Family and friend support for diabetes self-management serves as an important buffer. In patients with low family and friend support, more depressive symptoms at baseline were associated with subsequent worse glycemic levels (β = 0.36, critical ratio 4.03). In contrast, in individuals who had strong support, depressive symptoms did not predict subsequent glycemic control.

Conclusions: The present study provided evidence for the relationship between glycemic control and depression, finding that depressive symptoms predicted poorly controlled glycemic status, especially when the participants perceived inadequate support from their family or friends. A quick survey in clinics to assess the level of family or friend support for diabetes management and depressive symptoms might be an important part of individualized diabetic care.

INTRODUCTION

Type 2 diabetes mellitus is a complex, chronic illness affecting at least 415 million people worldwide. It is estimated that there will be 642 million people with diabetes by 2040[1]. Besides the well-known chronic microvascular and macrovascular complications of diabetes, dementia and depression are also associated with this condition. An approximately twofold increased prevalence of depression has been observed in people with diabetes compared with those without it[2]. Evidence suggests that the relationship between depression and diabetes might be bidirectional[3]. One analysis of prospective longitudinal studies found that depression is associated with a higher incidence of type 2 diabetes, accounting for a 60% increased risk[4]. However, in another longitudinal study, higher risk of incident diabetes was only observed in those individuals with both depressive symptoms and metabolic dysregulation, but not in those with

Received 13 August 2018; revised 15 October 2018; accepted 31 October 2018

depressive symptoms and without metabolic dysregulation[5]. A meta-analysis of longitudinal studies reported a 25% increased risk of incident depression in patients with type 2 diabetes[6]. Another population-based study also reported a 1.8-fold higher risk of incident depression in a diabetic group as compared with in an age- and sex-matched non-diabetic group[7]. However, prediabetes and undiagnosed diabetes have not been shown to be associated with subsequent incident depression[8]. The possible mechanism for increased risk of depression in patients with diabetes might be explained by the increased psychological burden of self-care, including managing macrovascular complications and hip fractures[9]. Longer duration of diabetes has also been linked to a higher risk of depression, which is also partially mediated by frailty[10]. In recent studies, the shared biochemical changes in depression and diabetes were also suggested as a possible explanation of their bidirectional relationship[11].

There have been many studies addressing the importance of comorbid depression in patients with diabetes because of the increase in microvascular complications, macrovascular complications[12], health service costs[13] and mortality[14] among these individuals. Better glycemic control results in better diabetes outcomes[15], as well as improved quality of life and economic benefits in newly diagnosed or longstanding type 2 diabetes[16]. Depression, which is associated with higher diabetes distress[17] and worse self-care behaviors, including physical inactivity, unhealthy diet and non-adherence to oral antidiabetic drugs, might be a barrier to better glycemic control[18]. Depression has also been associated with poor glycemic control in many cross-sectional studies[19].

However, previous studies investigating the causal relationship between glycemic control and depression have shown inconsistent results. A meta-analysis showed that depression is associated with non-adherence in patients with diabetes[20]. Medical non-adherence is known to be associated with unsatisfactory glycemic control[21]. A prospective study further elucidated that depression, but not sub-threshold depression, was associated with unsatisfactory glycemic control, medical non-adherence and problematic health-related behaviors in 1 year[22]. However, in a recent study focused on minority elderly patients with diabetes aged ≥55 years, depression was not associated with higher hemoglobin A1c (HbA1c) at baseline, nor was it at the 2-year follow up[23,24]. There have also been studies showing a significant improvement in HbA1c and psychological distress after non-pharmacological[25] or pharmacological management of depression[26]. However, a systemic review of 10 interventional studies found that psychosocial interventions only improve depressive symptoms, but not glycemic control[27]. There have been few studies examining the depression–HbA1c relationship in the inverse direction. It is suggested that glycemic control might predict depressive symptoms. A longitudinal study implied that past HbA1c variability, but not mean HbA1c, is associated with subsequent higher scores of depression in elderly patients with type 2 diabetes[28]. A short-term intensification of glycemic control was associated with improvements in depression, distress and quality of life, where depression was self-rated with five visual analog scales rather than a validated questionnaire[16].

It is possible that perceived support from family and friends plays a confounding role when studies attempt to investigate the causal relationship between depression and glycemic control. There is a modest positive relationship between family or friend support and diabetes management and successful management of chronic diseases, especially in the context of diabetes[29]. Social support in the community setting is also associated with healthy eating and physical activities that are essential for achieving better glycemic control[30]. Despite existing evidence suggesting that family support might affect glycemic control, no studies to our knowledge have examined the influence of diabetes-specific family or friend support in moderating the causal relationship between depression and glycemic control.

The present study builds on the current literature regarding depression and glycemic control. A structural equation model was constructed using longitudinal data from middle-aged and older participants in the Health and Retirement Study (HRS) and Diabetes-Specific Survey. We explored the directionality of the relationship between depressive symptoms and glycemic control, using family or friend support for diabetes management, health behavior (weight control, smoking and exercise) and sex as potential moderators.

METHODS

Participants

The present study included 398 middle-aged and elderly adults (aged ≥51 years at baseline) from the HRS with type 2 diabetes who had valid HbA1c values in the 2003 mail survey on diabetes, who continued follow up for the eighth waves (2006) of the core HRS and provided biomarker data. Details of the HRS core survey and 2003 mail survey on diabetes, including recruitment procedures and characteristics of the participants, have been described previously[31]. In brief, the HRS, beginning in 1992, is a biennial survey focusing on the long-term health status and retirement plans of community-dwelling middle-aged and elderly USA adults, with oversampling of Hispanics and African Americans. The 2003 mail survey followed adults with self-reported diabetes in one of the previous waves of the HRS core survey and collected data to achieve a more comprehensive understanding of all aspects associated with diabetes care and the impact of diabetes on individual personal life. Among the 1,901 adults who returned questionnaires, 1,233 (1,074 type 2 diabetes, 159 type 1 diabetes or uncertain) participants returned valid HbA1c assays. Diabetes type was self-reported by the participants. Among the 1,074 adults with type 2 diabetes, 676 who did not participate in the 2006 HRS core survey or did not provide valid HbA1c values were excluded from our analyses, resulting in a sample of 398 adults in the present study. The institutional review board at the University of

Michigan approved the methods and data collection in the HRS, and all participants provided informed consent before participating. The institutional review board at the National Cheng Kung University Hospital approved analysis of these data (B-ER-102-114). The access to the HRS database and HRS Sensitive Dataset is approved through online registration and application.

Measures

Depressive Symptoms

In the present study, depressive symptoms were measured at time 1 (T1; 2002) and time 2 (T2; 2006) with the Center for Epidemiologic Studies Depression Scale eight-item version, which has been shown to be a reliable measure for assessing the level of depressive symptoms in the elderly[32]. The items in the Center for Epidemiologic Studies Depression Scale 8 ask participants if they had experienced any of the following feelings much of the time during the past week: felt depressed, felt that everything was an effort, felt that their sleep was restless, were happy, felt lonely, enjoyed life, felt sad or were unable to get going. Responses for the eight-item Center for Epidemiologic Studies Depression Scale are yes or no for each item. The score range is 0–8. A cut-off value of 3 is indicative of depression.[33] The alpha coefficients of this scale were 0.82 and 0.84, respectively, at T1 and T2, showing good reliability in this sample.

Glycemic Control

The HbA1c level was used to determine glycemic control. The HbA1c was assessed by blood spot assays returned by the respondents to Flexsite Diagnostics.

Health Behavior

Among the health behaviors related to diabetes self-management, physical exercise[34], bodyweight control[35] and current smoking status[36], self-reported at baseline in 2002, were included in the study because these have been shown to influence glycemic control in adults with type 2 diabetes. Physical exercise behavior was examined with the following question: "On average over the last 12 months, have you participated in vigorous activity or exercise three times a week or more? By vigorous physical activity, we mean things like sports, heavy housework or a job that involves physical labor." Smoking behavior was assessed by asking respondents: "Do you smoke cigarettes now?" Bodyweight control was determined by the value of body mass index (BMI; kg/m^2), which was calculated by self-reported weight and height. Respondents with a BMI range within 18.5–29.9 were categorized as having good bodyweight control, whereas underweight (BMI <18.5) and obese participants (BMI of ≥30) were categorized as not having good bodyweight control. In order to estimate the overall moderating effects of health behaviors in the association between depressive symptoms and glycemic control, a composite index score was used – the sum of the presence of the three health behaviors (range 0–3). The higher the value of the composite scores, the more positive the health behavior was considered to be.

Family or Friend Support

Perceived diabetes-specific family or friend support was measured in the 2003 mail survey on diabetes with an eight-item scale, adapted from the Diabetes Care Profile[37]. Respondents used a 5-point Likert scale to rate if they could count on their family or friends to help and support them with planning meals, taking medicine, caring for their feet, engaging in physical activities, testing blood glucose, seeing the doctor, controlling weight and their feelings about diabetes. The respondents could reply to a statement with "strongly disagree," "disagree," "neutral," "agree" and "strongly agree," with these answers assigned values of 1, 2, 3, 4 and 5, respectively. The alpha coefficient for this scale was 0.96 in this sample. An average score of the eight items was obtained to indicate perceived family or friend support, with higher scores indicating greater perceived support. Participants were classified as being in the "high support" group if they had scores above the median (≥32). Those with scores below the median (≤31) were assigned to the "low support" group.

Statistical Analysis

To simultaneously address the reciprocal influences on glycemic control and depressive symptoms, we applied cross-lagged structural equation modeling. This is an approach widely used to infer causal associations in data from longitudinal research designs. First, measurement invariance was tested before testing this study's hypotheses (Figure S1). We carried out analyses to evaluate whether the factor structures of the key variables were the same across sex differences and support levels. Pairs of nested models were compared by means of χ^2 difference tests. We compared measurement models that constrained factor loadings to be the same across groups (i.e., different sex or participants based on their support levels) and models that allowed for differences between participants belonging to different groups. The χ^2 difference test was non-significant between groups of men and women, but was significant between those with high- and low-family support, suggesting invariant measurement across sex, and indicating that the factor structures of the key variables were significantly different for participants with high or low levels of perceived support. We thus proceeded with multigroup structural equation modeling to evaluate sex as a moderator, and tested our hypotheses for participants with high and low perceived support separately.

We report the standardized regression coefficients and critical ratios throughout. A critical ratio (CR) value of >1.96 was used to show a statistically significant path. The statistical analyses were carried out with the LISREL 8 program (Scientific Software International Inc., Skokie, IL, USA)[38]. Missing data were handled using full information maximum likelihood estimation with robust standard errors. Goodness of fit for our model was determined by χ^2 and three indices of practical fit: non-normed

fit index (NNFI/RHO), comparative fit indices and root mean square error of approximation. Values <0.05 for root mean square error of approximation, >0.95 for non-normed fit index and >0.96 for comparative fit indices are all indications of a good model fit.

RESULTS

The participants at baseline had a mean age of 67.9. The majority were white (81.7%), and 55.5% were women. The mean HbA1c in 2003 (T1) was 7.2%, ranging from 4.8% to 15.5%; the mean HbA1c in 2006 (T2) was 6.64%, ranging from 5.2% to 11.9%.

Descriptive Statistics

Health behaviors and depressive symptoms at T1 were different between men and women. Men had more of the health behaviors at baseline. There was no difference in glycemic control between men and women at either T1 or T2. Despite significantly fewer depressive symptoms at T1 in men, the Center for Epidemiologic Studies Depression Scale scores were similar at T2 (Table 1). Patients with higher perceived diabetes-specific family and friend support had more health behaviors (2.03 vs 1.81, $P < 0.01$), fewer depressive symptoms (1.23 vs 1.79, $P < 0.01$) and similar HbA1c levels (7.25% vs 7.18%) at T1 compared with those with lower support (Table 1). Patients having less family and friend support had lower HbA1c levels at T2 compared with those having higher support (6.55% vs 6.75%, $P < 0.05$; Table 1).

Intercorrelations

Table 2 presents the intercorrelations among each of the study variables separately for sex and for perceived family and friend support level, respectively. Depressive scores at T1 were positively associated with depressive scores at T2, with correlations ranging from 0.49 to 0.55. HbA1c levels at T1 were positively associated with HbA1c levels at T2, with correlations ranging from 0.41 to 0.55. These results show significantly moderate correlations on participants' 3-year re-examinations on both the depressive symptom scores and blood glucose levels.

Relationships that were only evident in women, but not in men, are listed as follows: health behaviors at T1 were correlated with depressive symptoms at T1 and T2; depressive symptoms at T1 were correlated with HbA1c levels at T1 and T2; HbA1c levels at T1 were correlated with depressive symptoms at T2.

Depressive symptoms at T1 and T2 were correlated with health behaviors at T1 in participants with both higher and lower support. However, the relationships that were only evident in the group with more support, but not in that with less support, were as follows: health behaviors and depressive symptoms at T1 were correlated with HbA1c levels at T1; HbA1c levels at T1 were correlated with depressive symptoms at T2. In contrast, depressive symptoms at T1 were only significantly correlated with HbA1c levels at T2 in the group with less support.

Multigroup Cross-Lagged Panel Analysis

Multigroup analysis assessing sex as a moderator was carried out by testing whether the strength of key associations among the study variables (i.e., T1 depressive symptoms to T2 HbA1c, and T1 HbA1c to T2 depressive symptoms) differed for men and women. We first fit a model in which the path coefficients were free to take on values that best fit the data for the two groups. We then set paths from T1 depressive symptoms to T2 HbA1c to be equated, and from T1 HbA1c to T2 depressive symptoms to be equated. These models suggest that men and women were not different in terms of these associations. As a result, we present all the path results together for both men and women (Figure 1).

Participants with high or low support were examined separately, but with the same procedures: we tested models with all structural parameters freely estimated at the beginning, and then we compared this model with other models deleting the path from T1 depressive symptoms to T2 HbA1c, deleting the path from T1 HbA1c to T2 depressive symptoms, and deleting both cross-lagged paths. The fit indices showed that in patients with diabetes and lower family and friend support, the depressive symptoms scores at T1 were significantly and positively

Table 1 | Descriptive statistics of main study variables for men and women and for individuals of high and low perceived support

Measure	Mean (SD)			Mean (SD)		
	Men (n = 177)	Women (n = 221)	t-test	High support (n = 196)	Low support (n = 202)	t-test
T1 Health behaviors	2.01 (0.81)	1.84 (0.81)	2.08*	2.03 (0.76)	1.81 (0.85)	2.64**
T1 Depressive symptoms	1.25 (1.90)	1.72 (2.11)	−2.28*	1.23 (1.78)	1.79 (2.23)	−2.71**
T1 HbA1c levels	7.16% (1.31)	7.26% (1.53)	−0.71	7.25% (1.42)	7.18% (1.45)	0.45
T2 depressive symptoms	1.38 (2.06)	1.71 (2.16)	−1.55	1.40 (1.98)	1.73 (2.25)	−1.58
T2 HbA1c levels	6.61% (0.91)	6.67% (1.08)	−0.61	6.75% (0.99)	6.55% (1.02)	2.00*

There is a significant difference between men and women in health behaviors and depressive symptoms scores at baseline. There is a significant difference between participants with high perceived support and participants with low perceived support in health behaviors and depressive symptom scores at baseline, and also hemoglobin A1c (HbA1c) level at 3-year follow up. *$P < 0.05$, **$P < 0.01$. T1, time 1; T2, time 2.

Table 2 | Correlation matrix for variables in the model by sex and perceived support level

Sex	Intercorrelations					Perceived support level	Intercorrelations				
Measure	1.	2.	3.	4.	5.		1.	2.	3.	4.	5.
1. T1 Health behaviors	–	−0.06	−0.06	−0.04	−0.03		–	−0.17*	−0.15*	−0.18**	−0.07
2. T1 Depressive symptoms	−0.22***	–	−0.03	0.49***	0.11		−0.14*	–	0.15*	0.49***	0.08
3. T1 HbA1c levels	−0.05	0.19**	–	0.01	0.47***		0.02	0.11	–	0.16*	0.41***
4. T2 depressive symptoms	−0.27***	0.55***	0.19**	–	0.06		−0.16*	0.55***	0.09	–	0.05
5. T2 HbA1c levels	0.03	0.20**	0.49***	0.07	–		0.03	0.28***	0.55***	0.11	–

For sex, the upper diagonal is based on men, whereas the lower diagonal is based on women. For perceived support level, the upper diagonal is based on the participants with high perceived support, whereas the lower diagonal is based on the participants with low perceived support. *$P < 0.05$, **$P < 0.01$; ***$P < 0.001$.

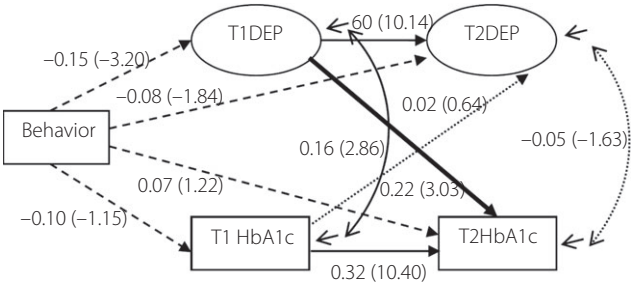

Figure 1 | Path coefficients for both men and women. The bold line shows that baseline depressive symptoms predict a worse hemoglobin A1c level during follow up. T1DEP, depressive symptoms at time 1; T1HbA1c, hemoglobin A1c at time 1; T2DEP, depressive symptoms at time 2; T2HbA1c, hemoglobin A1c at time 2.

associated with the subsequent glycemic level (β = 0.36, CR 4.03). However, in participants with strong family and friend support, depressive symptoms and HbA1c were correlated concurrently (β = 0.17, CR 2.24), but they did not predict each other 3 years later (Figure 2).

DISCUSSION

By using a two-wave panel design and cross-lagged structural equation modeling, the present study explored the predictive relationships between depressive symptoms and glycemic control in adults aged >50 years. In general, men and women did not differ in the depressive symptoms and glycemic control relationship, with a stronger association noted for higher depressive symptoms predicting worse glycemic control, rather than worse glycemic control predicting subsequent higher depressive symptom scores. Family and friend support for diabetes self-management was shown to buffer the negative effect of depression on glycemic control.

Consistent with a prior study that suggested depression is associated with medical non-adherence, problematic health-related behavior and unsatisfactory glycemic control at 12 months follow-up[22], the present findings provided evidence that more depressive symptoms are associated with higher subsequent HbA1C at 3-year follow up. Trajectories of depression shown in the literature also suggested that higher depressive symptoms at baseline tend to be persistently high during the follow-up years[39], that the effect on glycemic control might persist as well. Although higher depressive symptom score was associated with worse glycemic control, this relationship was attenuated by a high level of perceived support from family and friends. These findings suggested that family and friend support plays an important part in glycemic control, especially for those who experienced more depressive symptoms.

The role of family support in glycemic control has been emphasized in prior studies with controversial results, probably because of the heterogeneous definition on family support[40]. One study suggested that family support might improve

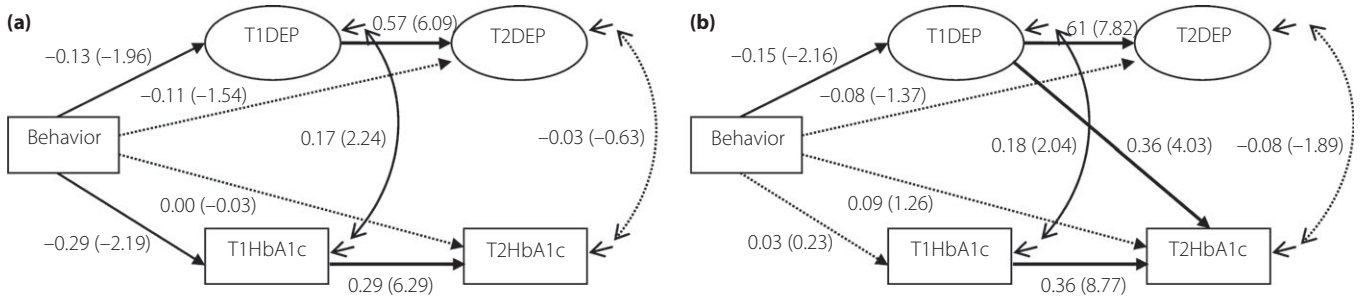

Figure 2 | Final structural models for people with (a) high and (b) low perceived support, showing standardized regression coefficients and their associated critical ratios. Broken lines represent paths that did not achieve statistical significance. Solid lines represent statistically significant paths. Single-headed arrows indicate directional associations; curved, double-headed arrows show covariation among variables assessed on the same occasion. T1DEP, depressive symptoms at time 1; T1HbA1c, hemoglobin A1c at time 1; T2DEP, depressive symptoms at time 2; T2HbA1c, hemoglobin A1c at time 2.

adherence[41], whereas another study reported no association between family support and self-management behaviors, such as following a diabetic-specific meal plan, engaging in physical activity, taking medicine and self-checking one's feet.[42] This study defined support by a patient being able to count on their family or friends to help and support with behaviors crucial for diabetes care. With more depressive symptoms, patients might need to count on their family and friends to manage their disease, including maintaining a healthy lifestyle, drug adherence and mental support.

Behavior of the family members might determine if a patient could count on them to help and support them for diabetes care. Mayberry *et al.*[43] found that more diabetic-specific supportive behaviors from family members were not associated with better HbA1c level. In contrast, more diabetic-specific non-supportive behaviors on the part of family members were associated with worse glycemic control. Family members engaging in more supportive behavior has also been associated with family members engaging in more non-supportive behavior[43]. The non-supportive behavior included "How often do your family members argue with you about your diabetes self-care activities?"[43] Individuals might not want to count on these family members to support them for diabetes care. In the present study, participants who could not count on their family could still control their blood glucose within the optimal range if they had few depressive symptoms. These participants were likely to be highly motivated or to have high diabetes self-efficacy. Earlier studies have shown that higher self-efficacy is associated with better glycemic control, better medication adherence, more self-care behavior and improved mental health-related quality of life[44]. The present analysis provides a possible explanation for the contradictory results of the previous studies exploring the association of family support and glycemic control. Family support in diabetes management is only beneficial for those who have a high burden of depressive symptoms, but not for those who have few depressive symptoms.

In accordance with previous studies showing that depression is negatively associated with social support and regular exercise[45], depressed patients with diabetes and a social network that offers a low level of support are likely to have poorer glycemic control, which is partially mediated by a decreased level of physical activity. If individuals can count on their family and friends for help with diabetes care, depression would not necessarily lead to worsened glycemic control. Encouraging family members to support glycemic control behavior by engaging in such things as helping them maintain drug adherence and exercising with them would be a strategy to help such patients to cope with the high burden of depressive symptoms.

The strengths of the present study are that it included a large set of national data, considered both sex and family or friend support as potential moderators for a depression–A1c association, and controlled for health behaviors, thus making the results more accurate. Using the rather complex analyses, we were able to clarify some of the mixed findings in longitudinal studies regarding the relationship between depression and glycemic control. The results of the present study contradict some earlier research that found that worse glycemic control predicts subsequent depression. This might be because the time interval between the two measures was too long to see the impact of glycemic control on depression.

There were also some limitations to the present study. First, health behaviors were not assessed at follow up, in that such behaviors might change over 3 years. Furthermore, the health behaviors were defined through a self-rated questionnaire rather than direct measurement or in-depth interviews. Second, the participants who were qualified for this analysis mostly had near optimal glycemic control, which might not represent all patients with type 2 diabetes. As participants who did not provide valid HbA1c values in 2006 were excluded from the analysis, remaining participants might be somewhat self-selected for adherence to the protocol. As a result, those who are willing to provide HbA1c value during the follow-up period had a

generally improved HbA1c level. Third, personal traits and the degree of intimacy with family and friends with the patient were not mentioned in the present study. A warm, accepting and close family member is reported to be associated with better patient adherence[41]. Finally, self-efficacy was not evaluated in this study, although this has been reported to be an important factor in maintaining good glycemic control.

Given the increasing incidences of both diabetes and depression, the results of the present study can encourage physicians to pay more attention to their patients' family and friend support, and depression status. Patient depression could contribute to poorly controlled glycemic status, especially when there is inadequate support from family or friends. More depressive symptoms will not predict worse glycemic control if participants can count on their family and friends to help and support them manage their diabetes. A quick survey in clinics to assess the level of family or friends support for diabetes management and depressive symptoms might thus be an important part of individualized diabetic care.

ACKNOWLEDGMENTS

The Health and Retirement Study data is sponsored by the National Institute on Aging (grant number U01AG009740) and is carried out by the University of Michigan. This analysis was supported by a grant from the Ministry of Science and Technology in Taiwan (P.I.: Ching-Ju Chiu PhD. Grant number: NSC 102-2314-b-006-075).

DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1| Cross-lagged regression model (hypothesized full model).