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Complete List of Authors:	Wen, Yue; West China Hospital, Sichuan University, Department of Gastrointestinal Surgery Liao, Jing; West China Hospital, Sichuan University, Department of Gastrointestinal Surgery Yin, Yiqiong; West China Hospital, Sichuan University, Gastrointestinal Department Liu, Chunjuan; West China Hospital, Sichuan University, Department of Gastrointestinal Surgery Gong, Renrong; Sichuan University Wu, Dongmei; University of Electronic Science and Technology of China, The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation; The Fourth People's Hospital of Chengdu & Chengdu Mental Health Center, Psychiatric Research Laboratory
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Risk of falls in four years of follow-up among Chinese adults with diabetes: Findings from the China Health and Retirement Longitudinal Study

Yue Wen, Jing Liao, Yiqiong Yin, Chunjuan Liu ,Renrong Gong*, Dongmei Wu*

Correspondence should be made to:

Dongmei Wu, PhD, RN

Associate professor

Department of Nursing, The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China

Huli West 1st Lane, Chengdu, Sichuan Province, China, 610036.

Tel: 86-28-69515754

E-mail: wudongmei_2001@163.com

Renrong Gong, BN, RN

Head Nurse, Department of Surgery Nursing, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041.

E-mail: gongrenrong@wchscu.cn

Tel：86-28-85421887

*: Renrong Gong and Dongmei Wu were co-corresponding authors for this manuscript.

The full names, institutions, city, and country of all other co-authors:

Yue Wen, BN, RN

Supervisor Nurse, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041.

E-mail: wenyue19820327@163.com

Jing Liao, MSN, RN, Senior Nurse, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041.

E-mail: m15982277765@163.com

Yiqiong Yin, BN, RN, Chief Superintendent Nurse, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041.

E-mail: yiqiong489@163.com

Chunjuan Liu,, Master of nursing, RN, Associate professor nurse, West China School of Nursing, Sichuan University/ West China Hospital, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041

E-mail: liuchunjuan2002@163.com

Renrong Gong, BN, RN, Head Nurse, Department of Surgery Nursing, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041. E-mail: gongrenrong@wchscu.cn

Tel：86-28-85421887

Dongmei Wu, PhD, RN, Associate professor, Department of Nursing, The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China

Huli West 1st Lane, Chengdu, China, 610036.

Tel: 86-28-69515754.

E-mail: wudongmei_2001@163.com

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Abstract

Objectives. The objectives of this study were to determine the incidence of falls and whether baseline risk factors increased a heightened risk for incident falls over time among people with diabetes.

Design. This study was a secondary analysis using the baseline and four years of follow-up data from the China Health and Retirement Longitudinal Study (CHARLS).

Setting. Chinese residents aged 45 and older were recruited in the baseline national wave of CHARLS, which was fielded in 2011 and included about 17,500 individuals in 150 counties in urban areas and 450 villages in rural areas. These participants were followed up every two years.

Participants. A total of 1238 middle-aged and older adults with diabetes and no history of falls at baseline were included in the current study.

Primary and secondary outcome measures. Information on incidence of falls and medical treatment resulting from falls were determined by self-report.

Results. The findings showed that the incidence of falls was 29.4% during four years of follow-up. Participants with incident falls were younger, were more likely to be women, had lower education level, and were less likely to be current drinkers. In addition, former drinkers were 2.22 times more likely to fall. Every 5 kg increase in grip strength was associated with a 13% lower risk of falls. A 10 mg/dL higher total cholesterol was associated with a 4% higher risk of falls. Finally, participants with depressive symptoms were 1.47 times more likely to fall compared to those without depressive symptoms.

Conclusions. These findings underscore the importance of developing a fall prevention program for those with diabetes, and this program should address potentially modifiable risk factors, including levels of total cholesterol, depressive symptoms, and grip strength.

Key words: incidence, falls, diabetes, middle-aged and older adults

Strengths and limitations of this study

- We used a national representative sample of participants with diabetes. Therefore, findings of our study can be generalized to adults with diabetes in China.
- Fall events were determined by self-report. However, several studies indicated that self-reported recall of falls by older adults may lead to underreporting since they may perceive a fall differently than researchers or health care providers. Therefore, there might be recall bias in the current study.
- This study examined the prospective relationships of baseline risk factors for falls with fall events in a four-year follow-up, and therefore no causal associations between these risk factors and fall events can be drawn from the current study.

Introduction

China is now home to the world's largest number of people with diabetes, with a report of 109.6 million adults having diabetes.[1,2] The prevalence of diabetes increases with age, and an estimate of about 20.2% of adults over 60 years of age were diabetic in 2013.[2] Recently, emerging evidence suggests that diabetes is associated with an increased risk of falls among older adults, especially for insulin users.[3] The underlying mechanisms may lie in the diabetes-related pathological changes, which may include vestibular dysfunction, peripheral neuropathy, diabetic retinopathy, declines in muscle strength, and severe hypoglycemic events associated with insulin use.[4,5] Falls are common in older adults with diabetes, with annual incidence rates of 39% among individuals aged 65 years or older and occurring more often in those with poor glycemic control.[6] Since falls are the leading cause of injury in older adults and can lead to decreased functional independence and lower quality of life,[7] it is critical to identify predictors that can be easily used to assess fall risks in the clinical settings among older adults with diabetes.

Recently, a few studies have examined risk factors that are associated with risk of falls among individuals with diabetes. For example, using data from the 2010 wave of the Health and Retirement Study, Blackwood[8] found that cognitive dysfunction, impairment in executive function and delayed recall, was associated with an increased risk for falls among the entire sample of older diabetics over 65 years of age and among a subsample of diabetics over 75 years of age, respectively. People receiving diabetes treatment, specially insulin users, had a significantly higher risk of falls (relatively risk=1.94) compared to non-insulin users (relative risk=1.27).[9] Other risk factors include depressive symptoms,[10] reduced physical performance (e.g., walking speed,[11] repeated chair stands,[12] and grip strength[13]), being overweight/obese,[11]

and problems with instrumental activities of daily living (IADL).[14] Hypoglycemia[15] and vision impairment[16] that are associated with the disease also contribute diabetic fall risk. However, these studies were mainly cross-sectional or had limited follow-up time. Large cohort studies with longer follow-up time are needed to study factors associated with falls in older Chinese adults with diabetes. Meanwhile, associations between serum biomarkers and risk of falls are not well studied. Such prospective associations may provide valuable insights into how baseline health conditions may predict risk of falls in the follow-up periods and help develop effective strategies to address these risk factors during primary health care service. Therefore, the purpose of this study was to determine the incidence of falls and examine a comprehensive list of potential risk factors associated with falls in four years of follow-up among participants with diabetes of the China Health and Retirement Longitudinal Study (CHARLS).

Methods

Study Design

This was a secondary data analysis of prospective data from the CHARLS. The CHARLS is an ongoing, biannual national survey, sponsored by the National Natural Science Foundation of China, the National Institute on Aging, and the World Bank.[17] The CHARLS questionnaire collects a substantial data on an individual's sociodemographic information, family structure, biomarkers, health status, physical performance, health insurance, employment history, retirement and pension, individual and household assets, and community level information.[17] Participants were selected using a multistage, stratified, cluster probability sampling strategy.[18] The sampling strategy has been previously described in detail,[19] and the study data sets can be downloaded at the CHARLS home page at http://charls.pku.edu.cn/en. A representative sample of 17,314 community-dwelling individuals of 45 years or older across the country was recruited

into the baseline wave of CHARLS, which was fielded in 2011 to 2012. The current analysis used data from baseline, the first, and the second follow-up surveys.

Study Sample

CHARLS participants with diabetes who had no history of falls and had complete data on age, gender, education level, falls, cognitive measures, body weight, height, walking speed, standing balance test, depressive symptoms, diabetes treatment, and plasma biomarkers at the time of the baseline survey were included in the current study. The final sample included in this study consisted of 1238 Chinese adults with diabetes.

The diagnosis of diabetes was based on a self-report of taking hypoglycemic agents (i.e., insulin use, or taking oral hypoglycemic medications including traditional Chinese, modern western medicine, or other diabetes treatment) as well as a blood sample reading specified by the American Diabetes Association:[20] fasting blood glucose ⩾126 mg/dL, or random blood glucose ⩾200 mg/dL, or HbA1c ⩾6.5%. Fasting venous blood samples were collected by trained health professionals on the day of physical examination. However, a small proportion (8%) of participants did not fast.[21] For those participants, random blood glucose and/or HbA1c were used to define diabetes.

Patient and Public Involvement

In the current study, we used de-identified data from the CHARLS with no direct involvement of or interaction with participants in the design, recruitment or conduct of the original cohort study.

Variables, Definitions, and Measures

Falls. Information on incidence of falls and medical treatment resulting from falls was collected in the CHARLS. The participant was asked if he/she had fallen down in the past two

years prior to the survey. If the participant answered "yes" to this question, he or she was then asked to indicate how many times falls resulted in a medical treatment.

Measurement of potential risk factors. Potential risk factors included demographics, lifestyle behaviors, depressive symptoms, physical health and functioning variables, biomarkers, cognitive function, and diabetes treatment. Demographics and lifestyle behaviors were measured based on self-report. Information on age, gender, marital status, and education levels was collected using face-to-face interviews. Marital status was categorized as married or separated. Education levels included no formal education/illiterate, some primary school, finish primary school, and junior high school or above. Lifestyle behaviors included smoking, drinking, and social activities. Smoking and drinking status were categorized as never, former and current users. Social activity was measured as no social activity, some social activity, and socially active.

Depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale (CES-D) short form.[22] The CES-D short form consists of ten items, and each item is rated on a four-point Likert scale ranging from 0 (rarely or none of the time) to 3 (most or all of the time) with a total possible summary score of 0 to 30.[22] Two positive symptoms (i.e., "was happy" and "hopeful about the future") were reversely coded before data analysis. The time frame refers to the week prior to the participants' interview date. The CES-D short form has been validated among a subsample of 742 CHARLS participants aged 60 years and older and has shown adequate psychometric properties. A CES-D score of 12 or higher was defined as having major depressive symptoms.[23]

Physical health and functioning variable included vision and hearing function, body mass index (BMI), repeated chair stand test, walking speed, grip strength, systolic blood pressure (SBP), and IADL. Vision and hearing impairments were self-reported by study participants. BMI

was calculated by dividing body weight in kilograms by the square of body height in meters, kg/m^2. To conduct repeated chair stand test, participants were asked to sit in the middle of the chair and place their hands on the opposite shoulder. Then they were asked to rise to a full standing position and sit back down again for five times. The examiner recorded the time if the participants finished the test without arms. If the participants must use their arms to stand, the examiner stopped the test, and recorded "0" for the number and score. The median time of five tests was used in the analysis. All participants aged 60 years or older without physical limitations that may interfere with walking were eligible for the test of walking speed. Participants were instructed to walk on a straight 2.5-meter flat course twice (there and back) at their normal walking speed. The examiner used a stopwatch to record the elapsed time necessary to walk the distance. The median time of the two tests was used as a measure of walking speed.[24,25] A hand-held dynamometer was used to assess grip strength. Participants were instructed to squeeze the dynamometer with all of their strength for a few seconds, typically twice with each hand, and alternate hands between tests. Consistent with a prior CHARLS publication,[26] an average score was calculated using the four measurements from both hands. IADL refers to meal preparation, doing housework, shopping, managing personal finances, and managing medications, and these activities were measured with scores ranging from 0 to 5.[27] Higher scores indicate having more difficulty in performing IADL, and loss of independence and mobility.

Biomarkers included blood lipids (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides), blood glucose (fasting glucose and hemoglobin A1c), creatinine, cystatin C, uric acid, blood urea nitrogen, C-reactive protein, hemoglobin, and hematocrit.

Subdomains of cognition measured in the CHARLS included visuospatial abilities, episodic memory, and orientation/attention. Consistent with prior CHARLS publications,[24,25] an overall cognitive score was calculated as a sum of these three cognitive subdomains, which could range from 0 to 21 and was used to indicate overall cognitive functioning of the participant.

Figure drawing. As previously presented by CHARLS,[24,25] the examiner first demonstrated a picture of two overlapping pentagons and the participant was required to draw a similar picture. Those who correctly drew the picture received a score of 1, while those who failed to draw the picture received a score of 0. This test was designed to measure a person's capacity to identify visual and spatial relationships among objects.

Word recall. This was a memory task for assessing both immediate and delayed recall. The immediate recall test involved presenting the participant with a list of 10 random words, which were read at a constant rate of 1 word every 2 seconds. At the end of the presentation, the participant was given up to 2 minutes to recall the list of words. Approximately 4 to 10 minutes later, a delayed recall test was administered by asking the participant to recall the list of 10 words presented earlier. For each task, the number of correctly recalled words was scored, with higher scores indicating better memory performance. In line with prior CHARLS publications,[24,25] an episodic memory score could range from 0 to 10 by averaging number of correctly recalled words from both immediate and delayed word tasks.

The Telephone Interview of Cognitive Status (TICS-10). The original TICS is a global mental status test that can either be administered over the telephone or face-to-face.[28] As previously presented by CHARLS,[24,25] ten questions from the original TICS were used in the CHARLS baseline survey, including date (day, month, and year), day of the week, the serial subtraction of 7 beginning with the number 100 up to five times, and season of the year. The

TICS-10 was used to assess orientation/attention, and it was calculated as the sum of correct answers which could range from 0 to 10.[29]

Treatment of diabetes was based on self-report. Participants were asked whether they took medications, including traditional Chinese medicine, modern medicine, and insulin, to treat diabetes. Participants that took any of the medications were coded as receiving anti-diabetic treatment.

Ethical Considerations

The CHARLS was approved by the Peking University Ethical Review Committee. The current study is a secondary analysis of the de-identified CHARLS public data. The Ethics Review Committee granted an exempt research determination to the current study.

Statistical Analysis

Baseline characteristics of the participants were summarized as mean and standard deviation or median and interquartile range for continuous variables and frequency and percentage for categorical variables. Binary associations between incidence of falls and potential risk factors at baseline were tested using Chi-squared tests for categorical variables and one-way analyses of variance (ANOVA) for continuous variables. Significant variables in the binary analyses were added in a multivariable logistic regression model to identify risk factors for fall. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were reported. The SAS 9.4 (SAS Institute Inc., Cary, North Carolina) was used to analyze the data. All p values were two-sided, and $p<0.05$ was considered significant.

Results

Characteristics of the Study Participants

A total of 1,238 participants with diabetes who reported no falls in the 2011 baseline visit were included in the current analyses, of whom, 364 (29.4%) reported to have fall(s) in 4 years of follow-up. As shown in Table 1, compared to participants had no incident fall, those with incident falls were younger (59.4 vs. 61.8), were more likely to be women (56.9% vs. 49.0%), had lower education level (illiterate rate: 33.2% vs. 24.9%), and were less likely to be current drinkers (13.8% vs. 21.6%). In addition, participants having incident fall(s) were more likely to be socially inactive (68.2% vs. 67.0%) and receive diabetes treatment (42.0% vs. 36.7%). However, these differences were not statistically significant (*P*=0.09 and 0.08 respectively). The two group of participants were similar in living areas, marital status, and smoking status.

Significant Variables in Bi-variable Analyses

In addition to age, gender, education level, and drinking status as described above, depressive symptoms, vision impairment, hearing problem, grip strength, IADL, total cholesterol, TICS-10, figure drawing, and total cognitive scores were also significantly associated with incident falls in the bi-variable analyses (Table 1).

Full-Model Results

When putting all significant variables identified in the bi-variable analyses in the full model, only drinking status, grip strength, total cholesterol, and depressive symptoms were significant predictors of incident fall(s). Vision impairment was a nominally significant predictor. Compared to never drinkers, former drinkers were 2.22 times (95% CI: 1.24 – 3.99) more likely to fall. However, current drinker had a similar risk as never drinkers (OR=1.11, 95% CI: 0.69 – 1.81). Every 5 kg increase in grip strength was associated with a 13% (95% CI: 2% - 21%) lower risk of falls. A 10 mg/dL higher total cholesterol was associated with a 4% (95% CI:

0% - 7%) higher risk of falls. Finally, participants with depressive symptoms were 1.47 (95% CI: 1.03-2.11) times more likely to fall compared to those without depressive symptoms.

Discussion

In this prospective analysis among this nationally representative sample of middle-aged and older Chinese diabetic participants without any history of fall(s), 29.4% reported to have incidence of falls in 4 years of follow-up. Compared to participants had no incident fall, those with incident falls were younger, were more likely to be women, had lower education attainment, and were less likely to be current drinkers. Furthermore, we identified four factors predicting risk for falls, including drinking status, grip strength, total cholesterol, and depressive symptoms. These findings will not only benefit allocation of health care resources to address health conditions, but also provide evidence for prevention strategies of falls in this population.

Alcohol consumption has been considered as a risk factor for falls by the World Health Organization, as physiological changes related to aging may increase sensitivity to alcohol use in older adults.[30] However, few studies have examined alcohol use as a risk for falls in community-dwelling older adults with diabetes. In this study, we found that former drinkers had a more than twice the risk of falls compared to never drinkers, however current drinkers had a similar risk as never drinkers. The findings are consistent with a previous study; in a large-scale study among 289,187 adults in the 2004-2013 U.S. National Health Interview Surveys, former drinker had a similar higher risk of falls as at-risk drinkers, compared to lifetime abstainers.[31] Furthermore, studies have shown that low-to-moderate drinking was associated with a reduced risk of fall.[32] In the CHARLS, about two thirds of the current drinkers were moderate drinkers (defined as having ≤14 drinks per week), and the remaining were at-risk drinkers (defined as having >14 drinks per week).[33] In the current study, current drinkers had a similar risk of fall as never drinkers. This may be a result of mixture of moderate and at-risk drinking. However, these are preliminary findings that need to be better investigated in future studies.

The hand grip strength is an indicator of muscle strength, which is important to fall prevention.[34] Grip strength was negatively associated with risk of falls in the current study, and this finding is intuitive and consistent with previous studies, which have repeatedly demonstrated a negative association between stronger grip strength and reduced fall events.[13,35-37] Our study provided further evidence that stronger grip strength at baseline was longitudinally associated with a less risk of falls in four-year follow-up among an older population with diabetes in China. In addition, hand grip strength has also been linked to other important diabetes outcomes. Using longitudinal data from the UK Biobank, Celis-Morales et al.[38] found that diabetics who had stronger grips had a reduced risk of all-cause mortality, lower risk of death from cardiovascular disease mortality, and less risk of developing cardiovascular disease. However, a decline in hand grip strength has been reported among individuals with diabetes compared to healthy individuals.[39] Taken together, these studies suggest that reduced grip strength may be used to identify a subgroup of patients with diabetes who are at a higher risk of falls and other important diabetes outcomes, and it is important to develop strategies to increase hand grip strength in this population.

Higher total cholesterol levels at baseline increased the risk of falls at follow-up in the current study. Previous studies that examined the relationship between biomarkers and fall risks have primarily focused on levels of high-density lipoprotein cholesterol,[40] which were not associated with fall events in the current study. Levels of total cholesterol are inversely associated with plasma 25-hydroxyvitamin D levels,[41] which are an important marker for frailty among Chinese community-dwelling older adults.[42] Levels of total cholesterol are also inversely associated with lean body mass,[43] which is important to determine risks of falls in older Asian adults.[44] However, plasma 25-hydroxyvitamin D and lean body mass were not measured in the CHARLS, so we were not able to examine whether these two biomarkers may explain the association between levels of total cholesterol and fall events in this study. Future studies of more biomarkers, such as metabolomics studies, may identify additional biomarkers and reveal underlying mechanisms of falls in this population.

The current study found that higher depressive symptoms may predict falls over time among individuals with diabetes. Such association has been widely reported in case-control, cross-sectional, and short-term prospective studies in the general populations.[45-48] Our study added further evidence with a larger sample size and a longer follow-up time among individuals with diabetes. Evidence suggested that baseline depressive symptoms increased fall risks through at least three different mechanisms. First, overall antidepressant use, particularly tricyclic antidepressants, are considered to contribute to falls because they increase sedation and risk of orthostatic hypotension.[49] Second, compared to the general population, patients with diabetes are more likely to experience depression.[50] A meta-analysis[51] demonstrated a significant association between depression and treatment non-adherence, including failing to engage in regular exercise among individuals with diabetes. As regular exercise contributes to muscle strength,[52] those who do not exercise regularly may have weaker muscle strength, which is associated with an increased risk of falls at follow-up. Third, depression and falls are also linked with each other through several common risk factors. Fear of falling, functional decline, history of falls, and cognitive dysfunction have been separately linked to both depression and falls.[46]

The findings of the current study have important implications for clinical practice. Given the high incidence of fall events (29.4%) among middle-aged and older adults with diabetes, it is important to develop a screening program with the goal of identifying at-risk and ensuring these individuals receive fall prevention programs. The identified risk factors, including drinking status, hand grips strength, blood lipids, and depressive symptoms, should be integrated into the screening program. In addition, as symptoms of depression are a potentially modifiable risk factor for falls, they should be addressed in fall prevention programs. Treatment of depressive symptoms by non-pharmacological approaches, such as physical exercise or psychosocial therapies such as mindfulness, should be considered as part of fall prevention programs in this high-risk population for falls.[53] Interventions to reduce the likelihood of falls among individuals with diabetes who have weak grip strength should focus on a combination of physical exercise, including resistance[52] and aerobic training exercises,[54] which has been shown to improve grip strength in patients with diabetes. Fall prevention programs should also target reducing levels of total cholesterol, as these individuals were at a higher risk of falls. Participants should be advised to first make lifestyle changes to improve cholesterol, including diet changes and increasing physical activity.

This study has several important strengths. A major strength of our study is that we used a national representative sample of participants with diabetes. Therefore, findings of our study can be generalized to persons with diabetes in China. In addition, we have also evaluated a comprehensive list of risk factors to predict fall events in 4 years of follow-up. Previous studies of falls have focused on limited number of factors.[8-16] Furthermore, a prospective cohort design was used, which avoided temporal ambiguity of potential factors and falls, and reduced survival bias, in which, an identified factor may be a result of fall rather than a risk factor. Finally, to ensure data integrity and validity, quality assurance measures have been implemented throughout the process of data collection in the CHARLS. These measures include reviewing data collection forms for completeness and accuracy of the data, verifying accuracy of data in electronic databases, as well as calling back participants.[18]

Our study also has limitations that need to be acknowledged. As in all population-based studies, fall events were determined by self-report. Previous research consistently showed that older adults tended to underreport falls because they did not recognize the severity of a fall or did not remember a fall with less severe consequences.[55] Therefore, there might be recall bias, and we should expect that the fall events may be underreported by participants in the current study. A prospective design with "daily fall calendar" is considered the golden standard to measure fall events,[55] and this method should be incorporated into future studies to more accurately capture fall events among individuals with diabetes. Another limitation of the study is that information on number of glucose-lowering medications was not collected. Therefore, we could not assess whether number of medications may be a risk factor for fall risks in this population. Finally, this study examined the prospective relationships of baseline risk factors for falls with fall events in four-year follow-up, and therefore no causal associations between these risk factors and fall events can be drawn from the current study.

Conclusions

To conclude, through a longitudinal study among a nationally representative sample of middle-aged and older participants with diabetes, we estimated that the incidence of fall events in 4 years of follow-up was as high as 29.4%. We also identified four factors predicting fall events. Besides the three risk factors (i.e., alcohol drinking, grip strength, and depressive symptoms), that have been reported in previous case-control, cross-sectional, and/or short-term prospective studies, our study identified a novel risk factor (i.e., levels of total cholesterol) to predict fall events among individuals with diabetes. Future studies of more biomarkers, such as a metabolomics study, are warranted to identify additional biomarkers for and reveal underlying mechanisms of fall events among this vulnerable population.

Contributorship Statement

All authors contribute to the conception and design of this study. YW, JL, CL, and DW were responsible for the design, analysis, drafting and revision of this manuscript. RG and YY were responsible for interpretation of data and preparation of the manuscript.

Competing Interests Statement

None declared.

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Patient Consent for Publication

Not required.

Data Sharing Statement

The study used a public data from the CHARLS that were obtained from the CHARLS home page at http://charls.pku.edu.cn/en.

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Tables

Table 1. Baseline characteristics of diabetic participants of the China Health and Retirement Longitudinal Study (CHARLS) according to incidence of fall in 4 years follow-up (2011-2015).

Variable	Incident Fall (n=364)	No Fall (n=874)	*P*
Demographics			
Age	59.4 (9.3)	61.8 (9)	**<.001**
Male, n (%)	157 (43.1%)	446 (51.0%)	**0.01**
Rural, n (%)	278 (76.4%)	655 (74.9%)	0.59
Married, n (%)	316 (86.8%)	784 (89.6%)	0.16
Education groups, n (%)			**0.02**
No formal education/illiterate	120 (33.2%)	218 (24.9%)	
Some primary school	61 (16.9%)	161 (18.4%)	
Finish primary school	78 (21.6%)	193 (22.1%)	
Junior high school or above	102 (28.3%)	302 (34.6%)	
Lifestyle behaviors			
Smoking, n (%)			0.41
Nonsmokers	230 (63.5%)	523 (59.9%)	
Former Smokers	45 (12.4%)	109 (12.5%)	
Current Smokers	87 (24.0%)	241 (27.6%)	
Drinking status, n (%)			**0.01**
Never	258 (75.7%)	592 (71.3%)	
Former	36 (10.6%)	59 (7.1%)	
Current	47 (13.8%)	179 (21.6%)	
Social activities, n (%)			0.09
No social activity	225 (68.2%)	553 (67.0%)	
Some social activity	49 (14.9%)	94 (11.4%)	
Socially active	56 (17.0%)	179 (21.7%)	
Diabetes treatment, n (%)	153 (42.0%)	321 (36.7%)	0.08
Psychosocial variables			
Mean CES-D score (SD)	7.6 (6)	9.6 (6.9)	**<.001**
Depressive symptoms, n (%)	119 (36.2%)	198 (24.2%)	**<.001**
Physical health and function			
Vision impairment, n (%)	44 (12.1%)	71 (8.1%)	**0.03**
Hearing problem, n (%)	38 (10.4%)	47 (5.4%)	**0.001**
Mean body mass index (SD), kg/m2	24.9 (3.9)	24.5 (3.8)	0.13
Chair stand test	10.7 (4.2)	11.3 (4.7)	0.05
Mean walking speed (SD), meters/min	4.6 (2.4)	4.7 (2.4)	0.66
Mean grip strength (SD), kg	30.3 (10.8)	26.9 (9.5)	**<.001**
Mean IADL (SD)	4.6 (1)	4.3 (1.3)	**<.001**

Mean systolic blood pressure (SD), mmHg	134.5 (20.9)	135.6 (20.2)	0.47
Biomarkers, mean (SD)			
Cystatin C, mg/l	1 (0.3)	1 (0.3)	0.15
Blood Urea Nitrogen, mg/dl	15.7 (4.2)	16.1 (4.6)	0.13
Total Cholesterol, mg/dl	199.7 (43.2)	206.8 (48.7)	**0.02**
Creatinine, mg/dl	0.8 (0.2)	0.8 (0.2)	0.75
C-Reactive Protein, mg/l	3.6 (9)	3.5 (8)	0.98
Glucose, mg/dl	164.6 (61.9)	165.5 (73.5)	0.85
Glycated Hemoglobin, %	6.2 (1.6)	6.4 (1.7)	0.27
HDL Cholesterol, mg/dl	45.4 (16)	46 (16.5)	0.61
LDL Cholesterol, mg/dl	112.8 (40.9)	118 (39.9)	0.06
Triglycerides, mg/dl	201.6 (200.6)	212.7 (222)	0.42
Uric Acid, mg/dl	4.6 (1.3)	4.6 (1.4)	0.91
Hemoglobin, g/dl	14.6 (2.2)	14.6 (2.4)	0.93
Hematocrit	42.2 (6)	41.8 (6.2)	0.40
Cognitive function			
Mean TICS (SD)	6.9 (2.8)	6.1 (3)	**<.001**
Figure drawing, n (%)	189 (58.2%)	547 (67.8%)	**0.002**
Mean episodic memory (SD)	4 (1.5)	3.9 (1.4)	0.28
Mean total cognitive score (SD)	10.5 (4.4)	9.2 (4.6)	**<.001**

CES-D= Center for Epidemiologic Studies Depression Scale; HDL=high-density lipoprotein; LDL=low-density lipoprotein; TICS=telephone interview of cognitive status; SD=standard deviation.

Table 2. Associations between baseline potential risk factors and incidence of fall in 4 years follow-up (2011-2015) among diabetes participants of the China Health and Retirement Longitudinal Study (CHARLS).

Variables	OR (95% CI)	*P*
Age, per 1 year	1.01 (0.99 - 1.03)	0.52
Male vs. Female	0.99 (0.61 - 1.58)	0.95
Drinking status		**0.03**
Never drinker	reference	
Former drinker	2.22 (1.24 - 3.99)	
Current drinker	1.11 (0.69 - 1.81)	
Education groups		0.69
No formal education or illiterate	reference	
Some primary school (read and write)	0.79 (0.47 - 1.33)	
Finished primary school	1.02 (0.61 - 1.71)	
Junior high school or above	1.06 (0.62 - 1.81)	
Having hearing problem, Y vs. N	0.94 (0.54 - 1.65)	0.83
Having vision problem, Y vs. N	1.74 (0.97 - 3.10)	0.06
Instrumental activities of daily living, per unit	0.89 (0.75 - 1.05)	0.15
Grip strength, per 5 kg	0.87 (0.79 - 0.98)	**0.02**
Total cholesterol, per 10 mg/dL	1.04 (1.00 - 1.07)	**0.046**
TICS-10, per unit	1.00 (0.89 - 1.13)	0.99
Figure drawing, Y vs. N	1.12 (0.73 - 1.70)	0.60
Total cognitive score, per unit	0.96 (0.88 - 1.04)	0.34
Depressive symptoms, Y vs. N	1.47 (1.03 - 2.11)	**0.03**

CI=confidence interval; OR=odds ratio; TICS=telephone interview of cognitive status.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-12
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Risk of falls in four years of follow-up among Chinese adults with diabetes: Findings from the China Health and Retirement Longitudinal Study

Yue Wen, Jing Liao, Yiqiong Yin, Chunjuan Liu, Renrong Gong*, Dongmei Wu*

Correspondence should be made to:

Dongmei Wu, PhD, RN

Associate professor

Department of Nursing, The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China

Huli West 1st Lane, Chengdu, Sichuan Province, China, 610036.

Tel: 86-28-69515754

E-mail: wudongmei_2001@163.com

Renrong Gong, BN, RN

Head Nurse, Department of Surgery Nursing, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041.

E-mail: gongrenrong@wchscu.cn

Tel：86-28-85421887

*: Renrong Gong and Dongmei Wu were co-corresponding authors for this manuscript.

The full names, institutions, city, and country of all other co-authors:

Yue Wen, BN, RN

Supervisor Nurse, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041.

E-mail: wenyue19820327@163.com

Jing Liao, MSN, RN, Senior Nurse, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041.

E-mail: m15982277765@163.com

Yiqiong Yin, BN, RN, Chief Superintendent Nurse, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University
37 Guoxue Xiang Street, Chengdu, China, 610041.
E-mail: yiqiong489@163.com
Chunjuan Liu,, Master of nursing, RN, Associate professor nurse, West China School of Nursing, Sichuan University/ West China Hospital, Sichuan University
37 Guoxue Xiang Street, Chengdu, China, 610041
E-mail: liuchunjuan2002@163.com
Renrong Gong, BN, RN, Head Nurse, Department of Surgery Nursing, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University
37 Guoxue Xiang Street, Chengdu, China, 610041. E-mail: gongrenrong@wchscu.cn
Tel：86-28-85421887
Dongmei Wu, PhD, RN, Associate professor, Department of Nursing, The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China
Huli West 1st Lane, Chengdu, China, 610036.
Tel: 86-28-69515754.
E-mail: wudongmei_2001@163.com

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Abstract

Objectives. This study was to determine the incidence of falls and identify baseline factors increased risk for incident falls over time among people with diabetes.

Design. This study was a secondary analysis using the baseline and four years of follow-up data from the China Health and Retirement Longitudinal Study (CHARLS).

Setting. A nationally representative survey of 17,500 Chinese residents aged 45 and older were recruited in the baseline national survey in 2011. These participants were followed up every two years.

Participants. A total of 1238 middle-aged and older adults with diabetes and no history of falls at baseline were included in the current study.

Primary and secondary outcome measures. Information on incidence of falls and medical treatment resulting from falls were determined by self-report.

Results. The findings showed that the incidence of falls was 29.4% during four years of follow-up. Participants with incident falls were younger, were more likely to be women, had lower education level, and were less likely to be current drinkers. In addition, former drinkers were 2.22 times more likely to fall. Socially active individuals were 47% less likely to fall compared to those without social activities. Every 5 kg increase in grip strength was associated with a 13% lower risk of falls. A 10 mg/dL higher total cholesterol and 1 mg/dl higher blood urea nitrogen were associated with a 4% and 6% higher risk of falls. Finally, participants with depressive symptoms were 1.47 times more likely to fall compared to those without depressive symptoms.

Conclusions. These findings underscore the importance of developing a fall prevention program for those with diabetes, and this program should address potentially modifiable risk factors, including levels of total cholesterol, blood urea nitrogen, social activity, depressive symptoms, and grip strength.

Key words: incidence, falls, diabetes, middle-aged and older adults

Strengths and limitations of this study

- We used a national representative sample of participants with diabetes. Therefore, findings of our study can be generalized to adults with diabetes in China.
- Fall events were determined by self-report. However, several studies indicated that self-reported recall of falls by older adults may lead to underreporting since they may perceive a fall differently than researchers or health care providers. Therefore, there might be recall bias in the current study.
- This study examined the prospective relationships of baseline risk factors for falls with fall events in a four-year follow-up, and therefore no causal associations between these risk factors and fall events can be drawn from the current study.

Introduction

China is now home to the world's largest number of people with diabetes, with a report of 109.6 million adults having diabetes.[1, 2] The prevalence of diabetes increases with age, and an estimate of about 20.2% of adults over 60 years of age were diabetic in 2013.[2] Recently, emerging evidence suggests that diabetes is associated with an increased risk of falls among older adults, especially for insulin users.[3] The underlying mechanisms may lie in the diabetes-related pathological changes, which may include vestibular dysfunction, peripheral neuropathy, diabetic retinopathy, declines in muscle strength, and severe hypoglycemic events associated with insulin use.[4, 5] Falls are common in older adults with diabetes, with annual incidence rates of 39% among individuals aged 65 years or older and occurring more often in those with poor glycemic control.[6] Since falls are the leading cause of injury in older adults and can lead to decreased functional independence and lower quality of life,[7] it is critical to identify predictors that can be easily used to assess fall risks in the clinical settings among older adults with diabetes.

Recently, a few studies have examined risk factors that are associated with risk of falls among individuals with diabetes. For example, using data from the 2010 wave of the Health and Retirement Study, Blackwood[8] found that cognitive dysfunction, impairment in executive function and delayed recall, was associated with an increased risk for falls among the entire sample of older diabetes over 65 years of age and among a subsample of diabetess over 75 years of age, respectively. People receiving diabetes treatment, specially insulin users, had a significantly higher risk of falls (relatively risk=1.94) compared to non-insulin users (relative risk=1.27).[9] Other risk factors include depressive symptoms,[10] reduced physical performance (e.g., walking speed,[11] repeated chair stands,[12] and grip strength[13]), being overweight/obese,[11]

and problems with instrumental activities of daily living (IADL).[14] Hypoglycemia[15] and vision impairment[16] that are associated with the disease also contribute diabetic fall risk. However, these studies were mainly cross-sectional or had limited follow-up time. Large cohort studies with longer follow-up time are needed to study factors associated with falls in older Chinese adults with diabetes. Meanwhile, associations between serum biomarkers and risk of falls are not well studied. Such prospective associations may provide valuable insights into how baseline health conditions may predict risk of falls in the follow-up periods and help develop effective strategies to address these risk factors during primary health care service. Therefore, the purpose of this study was to determine the incidence of falls and examine a comprehensive list of potential risk factors associated with falls in four years of follow-up among participants with diabetes of the China Health and Retirement Longitudinal Study (CHARLS).

Methods

Study Design

This was a secondary data analysis of prospective data from the CHARLS. The CHARLS is an ongoing, biannual national survey, sponsored by the National Natural Science Foundation of China, the National Institute on Aging, and the World Bank.[17] The CHARLS questionnaire collects a substantial data on an individual's sociodemographic information, family structure, biomarkers, health status, physical performance, health insurance, employment history, retirement and pension, individual and household assets, and community level information.[17] Participants were selected using a multistage, stratified, cluster probability sampling strategy.[18] The sampling strategy has been previously described in detail,[19] and the study data sets can be downloaded at the CHARLS home page at http://charls.pku.edu.cn/en. A representative sample of 17,314 community-dwelling individuals of 45 years or older across the country was recruited

into the baseline wave of CHARLS, which was fielded in 2011 to 2012. The current analysis used data from baseline, the first, and the second follow-up surveys.

Study Sample

CHARLS participants with diabetes who had no history of falls and had complete data on age, gender, education level, falls, cognitive measures, body weight, height, walking speed, standing balance test, depressive symptoms, diabetes treatment, and plasma biomarkers at the time of the baseline survey were included in the current study. The final sample included in this study consisted of 1238 Chinese adults with diabetes.

The American Diabetes Association[20] criteria was used to define diabetes status. Specifically, participants were diagnosed with diabetes if self-reporting to take hypoglycemic agents (i.e., insulin use, or taking oral hypoglycemic medications including traditional Chinese, modern western medicine, or other diabetes treatment), fasting blood glucose ⩾126 mg/dL, or random blood glucose ⩾200 mg/dL, or HbA1c ⩾6.5%. Fasting venous blood samples were collected by trained health professionals on the day of physical examination. However, a small proportion (8%) of participants did not fast.[21] For those participants, random blood glucose and/or HbA1c were used to define diabetes.

Patient and Public Involvement

In the current study, we used de-identified data from the CHARLS with no direct involvement of or interaction with participants in the design, recruitment or conduct of the original cohort study.

Variables, Definitions, and Measures

Falls. Information on incidence of falls and medical treatment resulting from falls was collected in the CHARLS. The participant was asked if he/she had fallen down in the past two

years prior to the survey. If the participant answered "yes" to this question, he or she was then asked to indicate how many times falls resulted in a medical treatment.

Measurement of potential risk factors. Potential risk factors included demographics, lifestyle behaviors, depressive symptoms, physical health and functioning variables, biomarkers, cognitive function, and diabetes treatment. Demographics and lifestyle behaviors were measured based on self-report. Information on age, gender, marital status, and education levels was collected using face-to-face interviews. Marital status was categorized as married or separated. Education levels included no formal education/illiterate, some primary school, finish primary school, and junior high school or above. Lifestyle behaviors included smoking, drinking, and social activities. Smoking and drinking status were categorized as never, former and current users. Social activity was measured as no social activity, some social activity, and socially active.

Depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale (CES-D) short form.[22] The CES-D short form consists of ten items, and each item is rated on a four-point Likert scale ranging from 0 (rarely or none of the time) to 3 (most or all of the time) with a total possible summary score of 0 to 30.[22] Two positive symptoms (i.e., "was happy" and "hopeful about the future") were reversely coded before data analysis. The time frame refers to the week prior to the participants' interview date. The CES-D short form has been validated among a subsample of 742 CHARLS participants aged 60 years and older and has shown adequate psychometric properties. A CES-D score of 12 or higher was defined as having major depressive symptoms.[23]

Physical health and functioning variable included vision and hearing function, body mass index (BMI), repeated chair stand test, walking speed, grip strength, systolic blood pressure (SBP), and IADL. Vision and hearing impairments were self-reported by study participants. BMI

was calculated by dividing body weight in kilograms by the square of body height in meters, kg/m^2. To conduct repeated chair stand test, participants were asked to sit in the middle of the chair and place their hands on the opposite shoulder. Then they were asked to rise to a full standing position and sit back down again for five times. The examiner recorded the time if the participants finished the test without arms. If the participants must use their arms to stand, the examiner stopped the test, and recorded "0" for the number and score. The median time of five tests was used in the analysis. All participants aged 60 years or older without physical limitations that may interfere with walking were eligible for the test of walking speed. Participants were instructed to walk on a straight 2.5-meter flat course twice (there and back) at their normal walking speed. The examiner used a stopwatch to record the elapsed time necessary to walk the distance. The median time of the two tests was used as a measure of walking speed.[24, 25] A hand-held dynamometer was used to assess grip strength. Participants were instructed to squeeze the dynamometer with all of their strength for a few seconds, typically twice with each hand, and alternate hands between tests. Consistent with a prior CHARLS publication,[26] an average score was calculated using the four measurements from both hands. IADL refers to meal preparation, doing housework, shopping, managing personal finances, and managing medications, and these activities were measured with scores ranging from 0 to 5.[27] Higher scores indicate having more difficulty in performing IADL, and loss of independence and mobility.

Biomarkers included blood lipids (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides), blood glucose (fasting glucose and hemoglobin A1c), creatinine, cystatin C, uric acid, blood urea nitrogen, C-reactive protein, hemoglobin, and hematocrit.

Subdomains of cognition measured in the CHARLS included visuospatial abilities, episodic memory, and orientation/attention. Consistent with prior CHARLS publications,[24, 25] an overall cognitive score was calculated as a sum of these three cognitive subdomains, which could range from 0 to 21 and was used to indicate overall cognitive functioning of the participant.

Figure drawing. As previously presented by CHARLS,[24, 25] the examiner first demonstrated a picture of two overlapping pentagons and the participant was required to draw a similar picture. Those who correctly drew the picture received a score of 1, while those who failed to draw the picture received a score of 0. This test was designed to measure a person's capacity to identify visual and spatial relationships among objects.

Word recall. This was a memory task for assessing both immediate and delayed recall. The immediate recall test involved presenting the participant with a list of 10 random words, which were read at a constant rate of 1 word every 2 seconds. At the end of the presentation, the participant was given up to 2 minutes to recall the list of words. Approximately 4 to 10 minutes later, a delayed recall test was administered by asking the participant to recall the list of 10 words presented earlier. For each task, the number of correctly recalled words was scored, with higher scores indicating better memory performance. In line with prior CHARLS publications,[24, 25] an episodic memory score could range from 0 to 10 by averaging number of correctly recalled words from both immediate and delayed word tasks.

The Telephone Interview of Cognitive Status (TICS-10). The original TICS is a global mental status test that can either be administered over the telephone or face-to-face.[28] As previously presented by CHARLS,[24, 25] ten questions from the original TICS were used in the CHARLS baseline survey, including date (day, month, and year), day of the week, the serial subtraction of 7 beginning with the number 100 up to five times, and season of the year. The

TICS-10 was used to assess orientation/attention, and it was calculated as the sum of correct answers which could range from 0 to 10.[29]

Treatment of diabetes was based on self-report. Participants were asked whether they took medications, including traditional Chinese medicine, modern medicine, and insulin, to treat diabetes. Participants that took any of the medications were coded as receiving anti-diabetic treatment.

Ethical Considerations

The CHARLS was approved by the Peking University Ethical Review Committee. All participants provided signed written consent forms in the original CHARLS study.[21] The current study is a secondary analysis of the de-identified CHARLS public data. The Ethics Review Committee at University of Electronic Science and Technology of China granted an exempt research determination to the current study.

Statistical Analysis

Baseline characteristics of the participants were summarized as mean and standard deviation or median and interquartile range for continuous variables and frequency and percentage for categorical variables. Binary associations between incidence of falls and potential risk factors at baseline were tested using Chi-squared tests for categorical variables and one-way analyses of variance (ANOVA) for continuous variables. Significant variables in the binary analyses were added in a multivariable logistic regression model to identify risk factors for fall. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were reported. In a sensitivity analysis, we also include variables with a p value <0.15 into the full model. The SAS 9.4 (SAS Institute Inc., Cary, North Carolina) was used to analyze the data. All p values were two-sided, and p<0.05 was considered significant.

Results

Characteristics of the Study Participants

A total of 1,238 participants with diabetes who reported no falls in the 2011 baseline visit were included in the current analyses, of whom, 364 (29.4%) reported to have fall(s) in 4 years of follow-up. As shown in Table 1, compared to participants had no incident fall, those with incident falls were younger (59.4 vs. 61.8), were more likely to be women (56.9% vs. 49.0%), had lower education level (illiterate rate: 33.2% vs. 24.9%), and were less likely to be current drinkers (13.8% vs. 21.6%). In addition, participants having incident fall(s) were more likely to be socially inactive (68.2% vs. 67.0%) and receive diabetes treatment (42.0% vs. 36.7%). However, these differences were not statistically significant (P=0.09 and 0.08 respectively). The two group of participants were similar in living areas, marital status, and smoking status.

Significant Variables in Bi-variable Analyses

In addition to age, gender, education level, and drinking status as described above, depressive symptoms, vision impairment, hearing problem, grip strength, IADL, total cholesterol, TICS-10, figure drawing, and total cognitive scores were also significantly associated with incident falls in the bi-variable analyses (Table 1).

Full-Model Results

As shown in Table 2, when putting all significant variables identified in the bi-variable analyses in the full model, only drinking status, grip strength, total cholesterol, and depressive symptoms were significant predictors of incident fall(s). Vision impairment was a nominally significant predictor. Compared to never drinkers, former drinkers were 2.22 times (95% CI:

1.24 – 3.99) more likely to fall. However, current drinker had a similar risk as never drinkers (OR=1.11, 95% CI: 0.69 – 1.81). Every 5 kg increase in grip strength was associated with a 13% (95% CI: 2% - 21%) lower risk of falls. A 10 mg/dL higher total cholesterol was associated with a 4% (95% CI: 0% - 7%) higher risk of falls. Finally, participants with depressive symptoms were 1.47 (95% CI: 1.03-2.11) times more likely to fall compared to those without depressive symptoms.

Furthermore, when adding all variables with a p<0.15 in the bi-variable analyses, p values for depressive symptoms (P=0.09) and total cholesterol (P=0.08) became nominally significant, however magnitudes of the associations did not change much. Furthermore, two new variables, social activity and blood urea nitrogen were significantly associated with risk of fall. Compared to people with no social activity, socially active individuals were 0.53 (95% CI: 0.31 – 0.91) times less likely to have fall. On contrary, one mg/dl higher blood urea nitrogen (BUN) was associated with 1.06 (95% CI: 1.01 - 1.11) times higher risk for fall.

Discussion

In this prospective analysis among this nationally representative sample of middle-aged and older Chinese diabetes participants without any history of fall(s), 29.4% reported to have incidence of falls in 4 years of follow-up. Compared to participants had no incident fall, those with incident falls were younger, were more likely to be women, had lower education attainment, and were less likely to be current drinkers. Furthermore, we identified four factors predicting risk for falls, including drinking status, grip strength, total cholesterol, and depressive symptoms. These findings will not only benefit allocation of health care resources to address health conditions, but also provide evidence for prevention strategies of falls in this population.

Alcohol consumption has been considered as a risk factor for falls by the World Health Organization, as physiological changes related to aging may increase sensitivity to alcohol use in older adults.[30] However, few studies have examined alcohol use as a risk for falls in community-dwelling older adults with diabetes. In this study, we found that former drinkers had a more than twice the risk of falls compared to never drinkers, however current drinkers had a similar risk as never drinkers. The findings are consistent with a previous study; in a large-scale study among 289,187 adults in the 2004-2013 U.S. National Health Interview Surveys, former drinker had a similar higher risk of falls as at-risk drinkers, compared to lifetime abstainers.[31] A possible reason could be that former drinkers might have stopped drinking due to poor health status which predisposed them to risk of fall. Furthermore, studies have shown that low-to-moderate drinking was associated with a reduced risk of fall.[32] In the CHARLS, about two thirds of the current drinkers were moderate drinkers (defined as having ≤14 drinks per week), and the remaining were at-risk drinkers (defined as having >14 drinks per week).[33] In the current study, current drinkers had a similar risk of fall as never drinkers. This may be a result of mixture of moderate and at-risk drinking. However, these are preliminary findings that need to be better investigated in future studies.

The hand grip strength is an indicator of muscle strength, which is important to fall prevention.[34] Grip strength was negatively associated with risk of falls in the current study, and this finding is intuitive and consistent with previous studies, which have repeatedly demonstrated a negative association between stronger grip strength and reduced fall events.[13, 35-37] Our study provided further evidence that stronger grip strength at baseline was longitudinally associated with a less risk of falls in four-year follow-up among an older population with diabetes in China. In addition, hand grip strength has also been linked to other important diabetes outcomes. Using longitudinal data from the UK Biobank, Celis-Morales et al.[38] found that diabetes patients who had stronger grips had a reduced risk of all-cause mortality, lower risk of death from cardiovascular disease mortality, and less risk of developing cardiovascular disease. However, a decline in hand grip strength has been reported among individuals with diabetes compared to healthy individuals.[39] Taken together, these studies suggest that reduced grip strength may be used to identify a subgroup of patients with diabetes who are at a higher risk of falls and other important diabetes outcomes, and it is important to develop strategies to increase hand grip strength in this population.

Higher total cholesterol and BUN levels at baseline increased the risk of falls at follow-up in the current study. Previous studies that examined the relationship between biomarkers and fall risks have primarily focused on levels of high-density lipoprotein cholesterol,[40] which were not associated with fall events in the current study. Levels of total cholesterol are inversely associated with plasma 25-hydroxyvitamin D levels,[41] which are an important marker for frailty among Chinese community-dwelling older adults.[42] Levels of total cholesterol are also inversely associated with lean body mass,[43] which is important to determine risks of falls in older Asian adults.[44] However, plasma 25-hydroxyvitamin D and lean body mass were not measured in the CHARLS, so we were not able to examine whether these two biomarkers may explain the association between levels of total cholesterol and fall events in this study. Since grip strength is correlated with lean body mass, we tried to evaluate total cholesterol and fall associations before and after controlling for grip strength, however, adding grip strength only slightly changed the effect of total cholesterol on fall. BUN reflects fluid depletion and is also influenced by protein intake, catabolism and tubular reabsorption.[45, 46] Dehydration is an important risk factor for fall and water intake could significantly reduce risk for fall in nursing homes.[47] However, in a case-control study among hospitalized patients, BUN was not associated fall.[46] Our study provided longitudinal evidence among a community dwelling older adults that higher BUN is associated with high risk for fall. Future studies of more biomarkers, such as metabolomics studies, may identify additional biomarkers and reveal underlying mechanisms of falls in this population.

The current study found that higher depressive symptoms may predict falls over time among individuals with diabetes. Such association has been widely reported in case-control, cross-sectional, and short-term prospective studies in the general populations.[48-51] Our study added further evidence with a larger sample size and a longer follow-up time among individuals with diabetes. Evidence suggested that baseline depressive symptoms increased fall risks through at least three different mechanisms. First, overall antidepressant use, particularly tricyclic antidepressants, are considered to contribute to falls because they increase sedation and risk of orthostatic hypotension.[52] Second, compared to the general population, patients with diabetes are more likely to experience depression.[53] A meta-analysis[54] demonstrated a significant association between depression and treatment non-adherence, including failing to engage in regular exercise among individuals with diabetes. As regular exercise contributes to muscle strength,[55] those who do not exercise regularly may have weaker muscle strength, which is associated with an increased risk of falls at follow-up. Third, depression and falls are also linked with each other through several common risk factors. Fear of falling, functional decline, history of falls, and cognitive dysfunction have been separately linked to both depression and falls.[49] However, due to social discrimination, depression was not routinely screened in clinical practice in China. Only a small proportion of patients with depressive symptoms (5-8%) were diagnosed with depression, and less than half of patients who were diagnosed with depression sought care over time.[56, 57] Our study highlighted the importance of screening depression to prevent fall among diabetes patients in China.

Socially active individuals also had lower risk of fall in the current study. This finding is consistent with previous studies, in which, social engagement could improve physical and mental health and reduce risk of fall.[58-61] In the current study, even after adjusting for physical and cognitive function measures, social activity was still associated with lower risk of fall. As hypothesized in previous studies, for socially active individuals, attention to environmental hazards and adaptation to changes in physical function may be triggered and encouraged by peers in social activities. Furthermore, socially active individuals may be more likely to get assistance from peers in routine or occasional tasks, such as reaching to an object on a high shelf during shopping.[58]

The findings of the current study have important implications for clinical practice. Given the high incidence of fall events (29.4%) among middle-aged and older adults with diabetes, it is important to develop a screening program with the goal of identifying at-risk and ensuring these individuals receive fall prevention programs. The identified risk factors, including drinking status, hand grips strength, blood lipids, and depressive symptoms, should be integrated into the screening program. In addition, as symptoms of depression are a potentially modifiable risk factor for falls, they should be addressed in fall prevention programs. Treatment of depressive symptoms by non-pharmacological approaches, such as physical exercise or psychosocial therapies such as mindfulness, should be considered as part of fall prevention programs in this high-risk population for falls.[62] Interventions to reduce the likelihood of falls among individuals with diabetes who have weak grip strength should focus on a combination of physical exercise, including resistance[55] and aerobic training exercises,[63] which has been shown to improve grip strength in patients with diabetes. Fall prevention programs should also target reducing levels of total cholesterol, as these individuals were at a higher risk of falls. Participants should be advised to first make lifestyle changes to improve cholesterol, including diet changes and increasing physical activity.

This study has several important strengths. A major strength of our study is that we used a national representative sample of participants with diabetes. Therefore, findings of our study can be generalized to persons with diabetes in China. In addition, we have also evaluated a comprehensive list of risk factors to predict fall events in 4 years of follow-up. Previous studies of falls have focused on limited number of factors.[8-16] Furthermore, a prospective cohort design was used, which avoided temporal ambiguity of potential factors and falls, and reduced survival bias, in which, an identified factor may be a result of fall rather than a risk factor. Finally, to ensure data integrity and validity, quality assurance measures have been implemented throughout the process of data collection in the CHARLS. These measures include reviewing data collection forms for completeness and accuracy of the data, verifying accuracy of data in electronic databases, as well as calling back participants.[18]

Our study also has limitations that need to be acknowledged. As in all population-based studies, fall events were determined by self-report. Previous research consistently showed that older adults tended to underreport falls because they did not recognize the severity of a fall or did not remember a fall with less severe consequences.[64] Therefore, there might be recall bias, and we should expect that the fall events may be underreported by participants in the current study. A prospective design with "daily fall calendar" is considered the golden standard to measure fall events,[64] and this method should be incorporated into future studies to more accurately capture fall events among individuals with diabetes. Another limitation of the study is that information on number of glucose-lowering medications was not collected. Therefore, we could not assess whether number of medications may be a risk factor for fall risks in this population.

Furthermore, some important and widely acknowledged risk factors, such as diabetic neuropathy and autonomic neuropathy were not measured in the CHARLS. We were not able to assess their contributions to fall in this population. Finally, this study examined the prospective relationships of baseline risk factors for falls with fall events in four-year follow-up, and therefore no causal associations between these risk factors and fall events can be drawn from the current study.

Conclusions

To conclude, through a longitudinal study among a nationally representative sample of middle-aged and older participants with diabetes, we estimated that the incidence of fall events in 4 years of follow-up was as high as 29.4%. We also identified four factors predicting fall events. Besides the five risk factors (i.e., alcohol drinking, grip strength, social activity, depressive symptoms, and BUN), that have been reported in previous case-control, cross-sectional, and/or short-term prospective studies, our study identified a novel risk factor (i.e., levels of total cholesterol) to predict fall events among individuals with diabetes. Future studies of more biomarkers, such as a metabolomics study, are warranted to identify additional biomarkers for and reveal underlying mechanisms of fall events among this vulnerable population.

Contributorship Statement

All authors contribute to the conception and design of this study. YW, JL, CL, and DW were responsible for the design, analysis, drafting and revision of this manuscript. RG and YY were responsible for interpretation of data and preparation of the manuscript.

Competing Interests Statement

None declared.

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Patient Consent for Publication

Not required.

Data Sharing Statement

The study used a public data from the CHARLS that were obtained from the CHARLS home page at http://charls.pku.edu.cn/en.

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Tables

Table 1. Baseline characteristics of diabetic participants of the China Health and Retirement Longitudinal Study (CHARLS) according to incidence of fall in 4 years follow-up (2011-2015).

Variable	Incident Fall (n=364)	No Fall (n=874)	*P*
Demographics			
Age	59.4 (9.3)	61.8 (9)	**<.001**
Male, n (%)	157 (43.1%)	446 (51.0%)	**0.01**
Rural, n (%)	278 (76.4%)	655 (74.9%)	0.59
Married, n (%)	316 (86.8%)	784 (89.6%)	0.16
Education groups, n (%)			**0.02**
No formal education/illiterate	120 (33.2%)	218 (24.9%)	
Some primary school	61 (16.9%)	161 (18.4%)	
Finish primary school	78 (21.6%)	193 (22.1%)	
Junior high school or above	102 (28.3%)	302 (34.6%)	
Lifestyle behaviors			
Smoking, n (%)			0.41
Nonsmokers	230 (63.5%)	523 (59.9%)	
Former Smokers	45 (12.4%)	109 (12.5%)	
Current Smokers	87 (24.0%)	241 (27.6%)	
Drinking status, n (%)			**0.01**
Never	258 (75.7%)	592 (71.3%)	
Former	36 (10.6%)	59 (7.1%)	
Current	47 (13.8%)	179 (21.6%)	
Social activities, n (%)			0.09
No social activity	225 (68.2%)	553 (67.0%)	
Some social activity	49 (14.9%)	94 (11.4%)	
Socially active	56 (17.0%)	179 (21.7%)	
Diabetes treatment, n (%)	153 (42.0%)	321 (36.7%)	0.08
Psychosocial variables			
Mean CES-D score (SD)	7.6 (6)	9.6 (6.9)	**<.001**
Depressive symptoms, n (%)	119 (36.2%)	198 (24.2%)	**<.001**
Physical health and function			
Vision impairment, n (%)	44 (12.1%)	71 (8.1%)	**0.03**
Hearing problem, n (%)	38 (10.4%)	47 (5.4%)	**0.001**
Mean body mass index (SD), kg/m2	24.9 (3.9)	24.5 (3.8)	0.13
Chair stand test	10.7 (4.2)	11.3 (4.7)	0.05
Mean walking speed (SD), meters/min	4.6 (2.4)	4.7 (2.4)	0.66
Mean grip strength (SD), kg	30.3 (10.8)	26.9 (9.5)	**<.001**

Mean IADL (SD)	4.6 (1)	4.3 (1.3)	**<.001**
Mean systolic blood pressure (SD), mmHg	134.5 (20.9)	135.6 (20.2)	0.47
Biomarkers, mean (SD)			
Cystatin C, mg/l	1 (0.3)	1 (0.3)	0.15
Blood Urea Nitrogen, mg/dl	15.7 (4.2)	16.1 (4.6)	0.13
Total Cholesterol, mg/dl	199.7 (43.2)	206.8 (48.7)	**0.02**
Creatinine, mg/dl	0.8 (0.2)	0.8 (0.2)	0.75
C-Reactive Protein, mg/l	3.6 (9)	3.5 (8)	0.98
Glucose, mg/dl	164.6 (61.9)	165.5 (73.5)	0.85
Glycated Hemoglobin, %	6.2 (1.6)	6.4 (1.7)	0.27
HDL Cholesterol, mg/dl	45.4 (16)	46 (16.5)	0.61
LDL Cholesterol, mg/dl	112.8 (40.9)	118 (39.9)	0.06
Triglycerides, mg/dl	201.6 (200.6)	212.7 (222)	0.42
Uric Acid, mg/dl	4.6 (1.3)	4.6 (1.4)	0.91
Hemoglobin, g/dl	14.6 (2.2)	14.6 (2.4)	0.93
Hematocrit	42.2 (6)	41.8 (6.2)	0.40
Cognitive function			
Mean TICS (SD)	6.9 (2.8)	6.1 (3)	**<.001**
Figure drawing, n (%)	189 (58.2%)	547 (67.8%)	**0.002**
Mean episodic memory (SD)	4 (1.5)	3.9 (1.4)	0.28
Mean total cognitive score (SD)	10.5 (4.4)	9.2 (4.6)	**<.001**

CES-D= Center for Epidemiologic Studies Depression Scale; HDL=high-density lipoprotein; LDL=low-density lipoprotein; TICS=telephone interview of cognitive status; SD=standard deviation.

Table 2. Associations between baseline potential risk factors and incidence of fall in 4 years follow-up (2011-2015) among diabetes participants of the China Health and Retirement Longitudinal Study (CHARLS).

Variables	Model 1		Model 2	
	OR (95% CI)	P	OR (95% CI)	P
Age, per 1 year	1.01 (0.99 - 1.03)	0.52	1.01 (0.98 - 1.04)	0.46
Male vs. Female	0.99 (0.61 - 1.58)	0.95	1.08 (0.61 - 1.94)	0.79
Drinking status				
Never drinker	reference	**0.03**	reference	**0.047**
Former drinker	2.22 (1.24 - 3.99)		2.32 (1.17 - 4.63)	
Current drinker	1.11 (0.69 - 1.81)		1.03 (0.57 - 1.86)	
Education groups				
No formal education or illiterate	reference	0.69	reference	0.91
Some primary school	0.79 (0.47 - 1.33)		1.25 (0.67 - 2.31)	
Finished primary school	1.02 (0.61 - 1.71)		1.19 (0.64 - 2.21)	
Junior high school or above	1.06 (0.62 - 1.81)		1.15 (0.60 - 2.20)	
Social activity				
No social activity	-		reference	**0.02**
Some social activity	-		1.42 (0.81 - 2.50)	
Socially active	-		0.53 (0.31 - 0.91)	
Diabetes treatment, Y vs. N (reference)	-		1.13 (0.75 - 1.73)	0.56
Depressive symptoms, Y vs. N (reference)	1.47 (1.03 - 2.11)	**0.03**	1.46 (0.95 - 2.26)	0.09
Having vision problem, Y vs. N (reference)	1.74 (0.97 - 3.10)	0.06	1.82 (0.92 - 3.61)	0.09
Having hearing problem, Y vs. N (reference)	0.94 (0.54 - 1.65)	0.83	0.88 (0.44 - 1.79)	0.73
BMI, per 1 kg/m2	-		0.98 (0.92 - 1.03)	0.38
Chair stand score, per unit	-		1.00 (0.96 - 1.05)	0.92
grip strength, per 5 kg	0.87 (0.79 - 0.98)	**0.02**	0.84 (0.73 - 0.96)	**0.01**
IADL, per unit	0.89 (0.75 - 1.05)	0.15	0.95 (0.77 - 1.17)	0.61
Cystatin C, per mg/l	-		0.79 (0.37 - 1.65)	0.52
Blood Urea Nitrogen, per mg/dl	-		1.06 (1.01 - 1.11)	**0.01**
Total cholesterol, per 10 mg/dL	1.04 (1.00 - 1.07)	**0.046**	1.05 (0.99 - 1.12)	0.08
Ldl Cholesterol, per mg/dl	-		1.00 (0.99 - 1.00)	0.39

TICS, per unit	1.00 (0.89 - 1.13)	0.99	1.00 (0.87 - 1.16)	0.98
Figure drawing, Y vs. N (reference)	1.12 (0.73 - 1.70)	0.60	0.95 (0.56 - 1.58)	0.83
Total cognitive score, per unit	0.96 (0.88 - 1.04)	0.34	1.00 (0.90 - 1.11)	0.94

CI=confidence interval; OR=odds ratio; TICS=telephone interview of cognitive status.

Note. Model included all variables with $p<0.05$ in univariate analyses; and model 2 included all variables with a $p<0.15$ in the univariate analyses.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-12
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Risk of falls in four years of follow-up among Chinese adults with diabetes: Findings from the China Health and Retirement Longitudinal Study

Yue Wen, Jing Liao, Yiqiong Yin, Chunjuan Liu, Renrong Gong*, Dongmei Wu*

Correspondence should be made to:

Dongmei Wu, PhD, RN

Associate professor

Department of Nursing, The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China

Huli West 1st Lane, Chengdu, Sichuan Province, China, 610036.

Tel: 86-28-69515754

E-mail: wudongmei_2001@163.com

Renrong Gong, BN, RN

Head Nurse, Department of Surgery Nursing, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041.

E-mail: gongrenrong@wchscu.cn

Tel：86-28-85421887

*: Renrong Gong and Dongmei Wu were co-corresponding authors for this manuscript.

The full names, institutions, city, and country of all other co-authors:

Yue Wen, BN, RN

Supervisor Nurse, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041.

E-mail: wenyue19820327@163.com

Jing Liao, MSN, RN, Senior Nurse, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041.

E-mail: m15982277765@163.com

Yiqiong Yin, BN, RN, Chief Superintendent Nurse, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University
37 Guoxue Xiang Street, Chengdu, China, 610041.
E-mail: yiqiong489@163.com
Chunjuan Liu,, Master of nursing, RN, Associate professor nurse, West China School of Nursing, Sichuan University/ West China Hospital, Sichuan University
37 Guoxue Xiang Street, Chengdu, China, 610041
E-mail: liuchunjuan2002@163.com
Renrong Gong, BN, RN, Head Nurse, Department of Surgery Nursing, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University
37 Guoxue Xiang Street, Chengdu, China, 610041. E-mail: gongrenrong@wchscu.cn
Tel：86-28-85421887
Dongmei Wu, PhD, RN, Associate professor, Department of Nursing, The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China
Huli West 1st Lane, Chengdu, China, 610036.
Tel: 86-28-69515754.
E-mail: wudongmei_2001@163.com

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Abstract

Objectives. This study was to determine the incidence of falls and identify baseline factors increased risk for incident falls over time among people with diabetes.

Design. This study was a secondary analysis using the baseline and four years of follow-up data from the China Health and Retirement Longitudinal Study (CHARLS).

Setting. A nationally representative survey of 17,500 Chinese residents aged 45 and older were recruited in the baseline national survey in 2011. These participants were followed up every two years.

Participants. A total of 1238 middle-aged and older adults with diabetes and no history of falls at baseline were included in the current study.

Primary and secondary outcome measures. Information on incidence of falls and medical treatment resulting from falls were determined by self-report.

Results. The findings showed that the incidence of falls was 29.4% during four years of follow-up. Participants with incident falls were younger, were more likely to be women, had lower education level, and were less likely to be current drinkers. In addition, former drinkers were 2.22 times more likely to fall. Socially active individuals were 47% less likely to fall compared to those without social activities. Every 5 kg increase in grip strength was associated with a 13% lower risk of falls. A 10 mg/dL higher total cholesterol and 1 mg/dl higher blood urea nitrogen were associated with a 4% and 6% higher risk of falls. Finally, participants with depressive symptoms were 1.47 times more likely to fall compared to those without depressive symptoms.

Conclusions. These findings underscore the importance of developing a fall prevention program for those with diabetes, and this program should address potentially modifiable risk factors, including levels of total cholesterol, blood urea nitrogen, social activity, depressive symptoms, and grip strength.

Key words: incidence, falls, diabetes, middle-aged and older adults

Strengths and limitations of this study

- We used a national representative sample of participants with diabetes. Therefore, findings of our study can be generalized to adults with diabetes in China.
- Fall events were determined by self-report. However, several studies indicated that self-reported recall of falls by older adults may lead to underreporting since they may perceive a fall differently than researchers or health care providers. Therefore, there might be recall bias in the current study.
- This study examined the prospective relationships of baseline risk factors for falls with fall events in a four-year follow-up, and therefore no causal associations between these risk factors and fall events can be drawn from the current study.

Introduction

China is now home to the world's largest number of people with diabetes, with a report of 109.6 million adults having diabetes.[1, 2] The prevalence of diabetes increases with age, and an estimate of about 20.2% of adults over 60 years of age were diabetic in 2013.[2] Recently, emerging evidence suggests that diabetes is associated with an increased risk of falls among older adults, especially for insulin users.[3] The underlying mechanisms may lie in the diabetes-related pathological changes, which may include vestibular dysfunction, peripheral neuropathy, diabetic retinopathy, declines in muscle strength, and severe hypoglycemic events associated with insulin use.[4, 5] Falls are common in older adults with diabetes, with annual incidence rates of 39% among individuals aged 65 years or older and occurring more often in those with poor glycemic control.[6] Since falls are the leading cause of injury in older adults and can lead to decreased functional independence and lower quality of life,[7] it is critical to identify predictors that can be easily used to assess fall risks in the clinical settings among older adults with diabetes.

Recently, a few studies have examined risk factors that are associated with risk of falls among individuals with diabetes. For example, using data from the 2010 wave of the Health and Retirement Study, Blackwood[8] found that cognitive dysfunction, impairment in executive function and delayed recall, was associated with an increased risk for falls among the entire sample of older diabetes over 65 years of age and among a subsample of diabetess over 75 years of age, respectively. People receiving diabetes treatment, specially insulin users, had a significantly higher risk of falls (relatively risk=1.94) compared to non-insulin users (relative risk=1.27).[9] Other risk factors include depressive symptoms,[10] reduced physical performance (e.g., walking speed,[11] repeated chair stands,[12] and grip strength[13]), being overweight/obese,[11]

and problems with instrumental activities of daily living (IADL).[14] Hypoglycemia[15] and vision impairment[16] that are associated with the disease also contribute diabetic fall risk. However, these studies were mainly cross-sectional or had limited follow-up time. Large cohort studies with longer follow-up time are needed to study factors associated with falls in older Chinese adults with diabetes. Meanwhile, associations between serum biomarkers and risk of falls are not well studied. Such prospective associations may provide valuable insights into how baseline health conditions may predict risk of falls in the follow-up periods and help develop effective strategies to address these risk factors during primary health care service. Therefore, the purpose of this study was to determine the incidence of falls and examine a comprehensive list of potential risk factors associated with falls in four years of follow-up among participants with diabetes of the China Health and Retirement Longitudinal Study (CHARLS).

Methods

Study Design

This was a secondary data analysis of prospective data from the CHARLS. The CHARLS is an ongoing, biannual national survey, sponsored by the National Natural Science Foundation of China, the National Institute on Aging, and the World Bank.[17] The CHARLS questionnaire collects a substantial data on an individual's sociodemographic information, family structure, biomarkers, health status, physical performance, health insurance, employment history, retirement and pension, individual and household assets, and community level information.[17] Participants were selected using a multistage, stratified, cluster probability sampling strategy.[18] The sampling strategy has been previously described in detail,[19] and the study data sets can be downloaded at the CHARLS home page at http://charls.pku.edu.cn/en. A representative sample of 17,314 community-dwelling individuals of 45 years or older across the country was recruited

into the baseline wave of CHARLS, which was fielded in 2011 to 2012. The current analysis used data from baseline, the first, and the second follow-up surveys.

Study Sample

CHARLS participants with diabetes who had no history of falls and had complete data on age, gender, education level, falls, cognitive measures, body weight, height, walking speed, standing balance test, depressive symptoms, diabetes treatment, and plasma biomarkers at the time of the baseline survey were included in the current study. The final sample included in this study consisted of 1238 Chinese adults with diabetes.

The American Diabetes Association[20] criteria was used to define diabetes status. Specifically, participants were diagnosed with diabetes if self-reporting to take hypoglycemic agents (i.e., insulin use, or taking oral hypoglycemic medications including traditional Chinese, modern western medicine, or other diabetes treatment), fasting blood glucose $\geqslant$126 mg/dL, or random blood glucose $\geqslant$200 mg/dL, or HbA1c $\geqslant$6.5%. Fasting venous blood samples were collected by trained health professionals on the day of physical examination. However, a small proportion (8%) of participants did not fast.[21] For those participants, random blood glucose and/or HbA1c were used to define diabetes.

Patient and Public Involvement

In the current study, we used de-identified data from the CHARLS with no direct involvement of or interaction with participants in the design, recruitment or conduct of the original cohort study.

Variables, Definitions, and Measures

Falls. Information on incidence of falls and medical treatment resulting from falls was collected in the CHARLS. The participant was asked if he/she had fallen down in the past two

years prior to the survey. If the participant answered "yes" to this question, he or she was then asked to indicate how many times falls resulted in a medical treatment.

Measurement of potential risk factors. Potential risk factors included demographics, lifestyle behaviors, depressive symptoms, physical health and functioning variables, biomarkers, cognitive function, and diabetes treatment. Demographics and lifestyle behaviors were measured based on self-report. Information on age, gender, marital status, and education levels was collected using face-to-face interviews. Marital status was categorized as married or separated. Education levels included no formal education/illiterate, some primary school, finish primary school, and junior high school or above. Lifestyle behaviors included smoking, drinking, and social activities. Smoking and drinking status were categorized as never, former and current users. Social activity was measured as no social activity, some social activity, and socially active.

Depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale (CES-D) short form.[22] The CES-D short form consists of ten items, and each item is rated on a four-point Likert scale ranging from 0 (rarely or none of the time) to 3 (most or all of the time) with a total possible summary score of 0 to 30.[22] Two positive symptoms (i.e., "was happy" and "hopeful about the future") were reversely coded before data analysis. The time frame refers to the week prior to the participants' interview date. The CES-D short form has been validated among a subsample of 742 CHARLS participants aged 60 years and older and has shown adequate psychometric properties. A CES-D score of 12 or higher was defined as having major depressive symptoms.[23]

Physical health and functioning variable included vision and hearing function, body mass index (BMI), repeated chair stand test, walking speed, grip strength, systolic blood pressure (SBP), and IADL. Vision and hearing impairments were self-reported by study participants. BMI

was calculated by dividing body weight in kilograms by the square of body height in meters, kg/m^2. To conduct repeated chair stand test, participants were asked to sit in the middle of the chair and place their hands on the opposite shoulder. Then they were asked to rise to a full standing position and sit back down again for five times. The examiner recorded the time if the participants finished the test without arms. If the participants must use their arms to stand, the examiner stopped the test, and recorded "0" for the number and score. The median time of five tests was used in the analysis. All participants aged 60 years or older without physical limitations that may interfere with walking were eligible for the test of walking speed. Participants were instructed to walk on a straight 2.5-meter flat course twice (there and back) at their normal walking speed. The examiner used a stopwatch to record the elapsed time necessary to walk the distance. The median time of the two tests was used as a measure of walking speed.[24, 25] A hand-held dynamometer was used to assess grip strength. Participants were instructed to squeeze the dynamometer with all of their strength for a few seconds, typically twice with each hand, and alternate hands between tests. Consistent with a prior CHARLS publication,[26] an average score was calculated using the four measurements from both hands. IADL refers to meal preparation, doing housework, shopping, managing personal finances, and managing medications, and these activities were measured with scores ranging from 0 to 5.[27] Higher scores indicate having more difficulty in performing IADL, and loss of independence and mobility.

Biomarkers included blood lipids (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides), blood glucose (fasting glucose and hemoglobin A1c), creatinine, cystatin C, uric acid, blood urea nitrogen, C-reactive protein, hemoglobin, and hematocrit.

Subdomains of cognition measured in the CHARLS included visuospatial abilities, episodic memory, and orientation/attention. Consistent with prior CHARLS publications,[24, 25] an overall cognitive score was calculated as a sum of these three cognitive subdomains, which could range from 0 to 21 and was used to indicate overall cognitive functioning of the participant.

Figure drawing. As previously presented by CHARLS,[24, 25] the examiner first demonstrated a picture of two overlapping pentagons and the participant was required to draw a similar picture. Those who correctly drew the picture received a score of 1, while those who failed to draw the picture received a score of 0. This test was designed to measure a person's capacity to identify visual and spatial relationships among objects.

Word recall. This was a memory task for assessing both immediate and delayed recall. The immediate recall test involved presenting the participant with a list of 10 random words, which were read at a constant rate of 1 word every 2 seconds. At the end of the presentation, the participant was given up to 2 minutes to recall the list of words. Approximately 4 to 10 minutes later, a delayed recall test was administered by asking the participant to recall the list of 10 words presented earlier. For each task, the number of correctly recalled words was scored, with higher scores indicating better memory performance. In line with prior CHARLS publications,[24, 25] an episodic memory score could range from 0 to 10 by averaging number of correctly recalled words from both immediate and delayed word tasks.

The Telephone Interview of Cognitive Status (TICS-10). The original TICS is a global mental status test that can either be administered over the telephone or face-to-face.[28] As previously presented by CHARLS,[24, 25] ten questions from the original TICS were used in the CHARLS baseline survey, including date (day, month, and year), day of the week, the serial subtraction of 7 beginning with the number 100 up to five times, and season of the year. The

TICS-10 was used to assess orientation/attention, and it was calculated as the sum of correct answers which could range from 0 to 10.[29]

Treatment of diabetes was based on self-report. Participants were asked whether they took medications, including traditional Chinese medicine, modern medicine, and insulin, to treat diabetes. Participants that took any of the medications were coded as receiving anti-diabetic treatment.

Ethical Considerations

The CHARLS was approved by the Peking University Ethical Review Committee. All participants provided signed written consent forms in the original CHARLS study.[21]
The current study is a secondary analysis of the de-identified CHARLS public data. The Ethics Review Committee at University of Electronic Science and Technology of China granted an exempt research determination to the current study.

Statistical Analysis

Baseline characteristics of the participants were summarized as mean and standard deviation or median and interquartile range for continuous variables and frequency and percentage for categorical variables. Binary associations between incidence of falls and potential risk factors at baseline were tested using Chi-squared tests for categorical variables and one-way analyses of variance (ANOVA) for continuous variables. Significant variables in the binary analyses were added in a multivariable logistic regression model to identify risk factors for fall. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were reported. In a sensitivity analysis, we also include variables with a p value <0.15 into the full model. The SAS 9.4 (SAS Institute Inc., Cary, North Carolina) was used to analyze the data. All p values were two-sided, and p<0.05 was considered significant.

Results

Characteristics of the Study Participants

A total of 1,238 participants with diabetes who reported no falls in the 2011 baseline visit were included in the current analyses, of whom, 364 (29.4%) reported to have fall(s) in 4 years of follow-up. As shown in Table 1, compared to participants had no incident fall, those with incident falls were younger (59.4 vs. 61.8), were more likely to be women (56.9% vs. 49.0%), had lower education level (illiterate rate: 33.2% vs. 24.9%), and were less likely to be current drinkers (13.8% vs. 21.6%). In addition, participants having incident fall(s) were more likely to be socially inactive (68.2% vs. 67.0%) and receive diabetes treatment (42.0% vs. 36.7%). However, these differences were not statistically significant (*P*=0.09 and 0.08 respectively). The two group of participants were similar in living areas, marital status, and smoking status.

Significant Variables in Bi-variable Analyses

In addition to age, gender, education level, and drinking status as described above, depressive symptoms, vision impairment, hearing problem, grip strength, IADL, total cholesterol, TICS-10, figure drawing, and total cognitive scores were also significantly associated with incident falls in the bi-variable analyses (Table 1).

Full-Model Results

As shown in Table 2, when putting all significant variables identified in the bi-variable analyses in the full model, only drinking status, grip strength, total cholesterol, and depressive symptoms were significant predictors of incident fall(s). Vision impairment was a nominally significant predictor. Compared to never drinkers, former drinkers were 2.22 times (95% CI:

1.24 – 3.99) more likely to fall. However, current drinker had a similar risk as never drinkers (OR=1.11, 95% CI: 0.69 – 1.81). Every 5 kg increase in grip strength was associated with a 13% (95% CI: 2% - 21%) lower risk of falls. A 10 mg/dL higher total cholesterol was associated with a 4% (95% CI: 0% - 7%) higher risk of falls. Finally, participants with depressive symptoms were 1.47 (95% CI: 1.03-2.11) times more likely to fall compared to those without depressive symptoms.

Furthermore, when adding all variables with a p<0.15 in the bi-variable analyses, p values for depressive symptoms (P=0.09) and total cholesterol (P=0.08) became nominally significant, however magnitudes of the associations did not change much. Furthermore, two new variables, social activity and blood urea nitrogen were significantly associated with risk of fall. Compared to people with no social activity, socially active individuals were 0.53 (95% CI: 0.31 – 0.91) times less likely to have fall. On contrary, one mg/dl higher blood urea nitrogen (BUN) was associated with 1.06 (95% CI: 1.01 - 1.11) times higher risk for fall.

Discussion

In this prospective analysis among this nationally representative sample of middle-aged and older Chinese diabetes participants without any history of fall(s), 29.4% reported to have incidence of falls in 4 years of follow-up. Compared to participants had no incident fall, those with incident falls were younger, were more likely to be women, had lower education attainment, and were less likely to be current drinkers. Furthermore, we identified four factors predicting risk for falls, including drinking status, grip strength, total cholesterol, and depressive symptoms. These findings will not only benefit allocation of health care resources to address health conditions, but also provide evidence for prevention strategies of falls in this population.

Alcohol consumption has been considered as a risk factor for falls by the World Health Organization, as physiological changes related to aging may increase sensitivity to alcohol use in older adults.[30] However, few studies have examined alcohol use as a risk for falls in community-dwelling older adults with diabetes. In this study, we found that former drinkers had a more than twice the risk of falls compared to never drinkers, however current drinkers had a similar risk as never drinkers. The findings are consistent with a previous study; in a large-scale study among 289,187 adults in the 2004-2013 U.S. National Health Interview Surveys, former drinker had a similar higher risk of falls as at-risk drinkers, compared to lifetime abstainers.[31] A possible reason could be that former drinkers might have stopped drinking due to poor health status which predisposed them to risk of fall. In the current study, compared to never drinkers, former drinkers were more likely to have vision impairment and take diabetes medications. It is possible that the vision impairment was due to worse glucose control, and former drinkers were highly suggested by doctors to take diabetes medications. Future studies with larger sample sizes, particularly for former drinkers, and more detailed measures of health status are warranted to further validate our findings. Nevertheless, studies have shown that low-to-moderate drinking was associated with a reduced risk of fall.[32] In the CHARLS, about two thirds of the current drinkers were moderate drinkers (defined as having ≤14 drinks per week), and the remaining were at-risk drinkers (defined as having >14 drinks per week).[33] In the current study, current drinkers had a similar risk of fall as never drinkers. This may be a result of mixture of moderate and at-risk drinking. However, these are preliminary findings that need to be better investigated in future studies.

The hand grip strength is an indicator of muscle strength, which is important to fall prevention.[34] Grip strength was negatively associated with risk of falls in the current study, and this finding is intuitive and consistent with previous studies, which have repeatedly demonstrated a negative association between stronger grip strength and reduced fall events.[13, 35-37] Our study provided further evidence that stronger grip strength at baseline was longitudinally associated with a less risk of falls in four-year follow-up among an older population with diabetes in China. In addition, hand grip strength has also been linked to other important diabetes outcomes. Using longitudinal data from the UK Biobank, Celis-Morales et al.[38] found that diabetes patients who had stronger grips had a reduced risk of all-cause mortality, lower risk of death from cardiovascular disease mortality, and less risk of developing cardiovascular disease. However, a decline in hand grip strength has been reported among individuals with diabetes compared to healthy individuals.[39] Taken together, these studies suggest that reduced grip strength may be used to identify a subgroup of patients with diabetes who are at a higher risk of falls and other important diabetes outcomes, and it is important to develop strategies to increase hand grip strength in this population.

Higher total cholesterol and BUN levels at baseline increased the risk of falls at follow-up in the current study. Previous studies that examined the relationship between biomarkers and fall risks have primarily focused on levels of high-density lipoprotein cholesterol,[40] which were not associated with fall events in the current study. Levels of total cholesterol are inversely associated with plasma 25-hydroxyvitamin D levels,[41] which are an important marker for frailty among Chinese community-dwelling older adults.[42] Levels of total cholesterol are also inversely associated with lean body mass,[43] which is important to determine risks of falls in older Asian adults.[44] However, plasma 25-hydroxyvitamin D and lean body mass were not measured in the CHARLS, so we were not able to examine whether these two biomarkers may explain the association between levels of total cholesterol and fall events in this study. Since grip strength is correlated with lean body mass, we tried to evaluate total cholesterol and fall associations before and after controlling for grip strength, however, adding grip strength only slightly changed the effect of total cholesterol on fall. BUN reflects fluid depletion and is also influenced by protein intake, catabolism and tubular reabsorption.[45, 46] Dehydration is an important risk factor for fall and water intake could significantly reduce risk for fall in nursing homes.[47] However, in a case-control study among hospitalized patients, BUN was not associated fall.[46] Our study provided longitudinal evidence among a community dwelling older adults that higher BUN is associated with high risk for fall. Future studies of more biomarkers, such as metabolomics studies, may identify additional biomarkers and reveal underlying mechanisms of falls in this population.

The current study found that higher depressive symptoms may predict falls over time among individuals with diabetes. Such association has been widely reported in case-control, cross-sectional, and short-term prospective studies in the general populations.[48-51] Our study added further evidence with a larger sample size and a longer follow-up time among individuals with diabetes. Evidence suggested that baseline depressive symptoms increased fall risks through at least three different mechanisms. First, overall antidepressant use, particularly tricyclic antidepressants, are considered to contribute to falls because they increase sedation and risk of orthostatic hypotension.[52] Second, compared to the general population, patients with diabetes are more likely to experience depression.[53] A meta-analysis[54] demonstrated a significant association between depression and treatment non-adherence, including failing to engage in regular exercise among individuals with diabetes. As regular exercise contributes to muscle strength,[55] those who do not exercise regularly may have weaker muscle strength, which is associated with an increased risk of falls at follow-up. Third, depression and falls are also linked with each other through several common risk factors. Fear of falling, functional decline, history of falls, and cognitive dysfunction have been separately linked to both depression and falls.[49] However, due to social discrimination, depression was not routinely screened in clinical practice in China. Only a small proportion of patients with depressive symptoms (5-8%) were diagnosed with depression, and less than half of patients who were diagnosed with depression sought care over time.[56, 57] Our study highlighted the importance of screening depression to prevent fall among diabetes patients in China.

Socially active individuals also had lower risk of fall in the current study. This finding is consistent with previous studies, in which, social engagement could improve physical and mental health and reduce risk of fall.[58-61] In the current study, even after adjusting for physical and cognitive function measures, social activity was still associated with lower risk of fall. As hypothesized in previous studies, for socially active individuals, attention to environmental hazards and adaptation to changes in physical function may be triggered and encouraged by peers in social activities. Furthermore, socially active individuals may be more likely to get assistance from peers in routine or occasional tasks, such as reaching to an object on a high shelf during shopping.[58]

The findings of the current study have important implications for clinical practice. Given the high incidence of fall events (29.4%) among middle-aged and older adults with diabetes, it is important to develop a screening program with the goal of identifying at-risk and ensuring these individuals receive fall prevention programs. The identified risk factors, including drinking status, hand grips strength, blood lipids, and depressive symptoms, should be integrated into the screening program. In addition, as symptoms of depression are a potentially modifiable risk factor for falls, they should be addressed in fall prevention programs. Treatment of depressive symptoms by non-pharmacological approaches, such as physical exercise or psychosocial therapies such as mindfulness, should be considered as part of fall prevention programs in this high-risk population for falls.[62] Interventions to reduce the likelihood of falls among individuals with diabetes who have weak grip strength should focus on a combination of physical exercise, including resistance[55] and aerobic training exercises,[63] which has been shown to improve grip strength in patients with diabetes. Fall prevention programs should also target reducing levels of total cholesterol, as these individuals were at a higher risk of falls. Participants should be advised to first make lifestyle changes to improve cholesterol, including diet changes and increasing physical activity.

This study has several important strengths. A major strength of our study is that we used a national representative sample of participants with diabetes. Therefore, findings of our study can be generalized to persons with diabetes in China. In addition, we have also evaluated a comprehensive list of risk factors to predict fall events in 4 years of follow-up. Previous studies of falls have focused on limited number of factors.[8-16] Furthermore, a prospective cohort design was used, which avoided temporal ambiguity of potential factors and falls, and reduced survival bias, in which, an identified factor may be a result of fall rather than a risk factor. Finally, to ensure data integrity and validity, quality assurance measures have been implemented throughout the process of data collection in the CHARLS. These measures include reviewing data collection forms for completeness and accuracy of the data, verifying accuracy of data in electronic databases, as well as calling back participants.[18]

Our study also has limitations that need to be acknowledged. As in all population-based studies, fall events were determined by self-report. Previous research consistently showed that older adults tended to underreport falls because they did not recognize the severity of a fall or did not remember a fall with less severe consequences.[64] Therefore, there might be recall bias, and we should expect that the fall events may be underreported by participants in the current study. A prospective design with "daily fall calendar" is considered the golden standard to measure fall events,[64] and this method should be incorporated into future studies to more accurately capture fall events among individuals with diabetes. Another limitation of the study is that information on number of glucose-lowering medications was not collected. Therefore, we could not assess whether number of medications may be a risk factor for fall risks in this population. Furthermore, some important and widely acknowledged risk factors, such as diabetic neuropathy and autonomic neuropathy were not measured in the CHARLS. We were not able to assess their contributions to fall in this population. Finally, this study examined the prospective relationships of baseline risk factors for falls with fall events in four-year follow-up, and therefore no causal associations between these risk factors and fall events can be drawn from the current study.

Conclusions

To conclude, through a longitudinal study among a nationally representative sample of middle-aged and older participants with diabetes, we estimated that the incidence of fall events in 4 years of follow-up was as high as 29.4%. We also identified four factors predicting fall events. Besides the five risk factors (i.e., alcohol drinking, grip strength, social activity, depressive symptoms, and BUN), that have been reported in previous case-control, cross-sectional, and/or short-term prospective studies, our study identified a novel risk factor (i.e., levels of total cholesterol) to predict fall events among individuals with diabetes. Future studies of more biomarkers, such as a metabolomics study, are warranted to identify additional biomarkers for and reveal underlying mechanisms of fall events among this vulnerable population.

Contributorship Statement

All authors contribute to the conception and design of this study. YW, JL, CL, and DW were responsible for the design, analysis, drafting and revision of this manuscript. RG and YY were responsible for interpretation of data and preparation of the manuscript.

Competing Interests Statement

None declared.

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Patient Consent for Publication

Not required.

Data Sharing Statement

The study used a public data from the CHARLS that were obtained from the CHARLS home page at http://charls.pku.edu.cn/en.

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Tables

Table 1. Baseline characteristics of diabetic participants of the China Health and Retirement Longitudinal Study (CHARLS) according to incidence of fall in 4 years follow-up (2011-2015).

Variable	Incident Fall (n=364)	No Fall (n=874)	*P*
Demographics			
Age	59.4 (9.3)	61.8 (9)	**<.001**
Male, n (%)	157 (43.1%)	446 (51.0%)	**0.01**
Rural, n (%)	278 (76.4%)	655 (74.9%)	0.59
Married, n (%)	316 (86.8%)	784 (89.6%)	0.16
Education groups, n (%)			**0.02**
No formal education/illiterate	120 (33.2%)	218 (24.9%)	
Some primary school	61 (16.9%)	161 (18.4%)	
Finish primary school	78 (21.6%)	193 (22.1%)	
Junior high school or above	102 (28.3%)	302 (34.6%)	
Lifestyle behaviors			
Smoking, n (%)			0.41
Nonsmokers	230 (63.5%)	523 (59.9%)	
Former Smokers	45 (12.4%)	109 (12.5%)	
Current Smokers	87 (24.0%)	241 (27.6%)	
Drinking status, n (%)			**0.01**
Never	258 (75.7%)	592 (71.3%)	
Former	36 (10.6%)	59 (7.1%)	
Current	47 (13.8%)	179 (21.6%)	
Social activities, n (%)			0.09
No social activity	225 (68.2%)	553 (67.0%)	
Some social activity	49 (14.9%)	94 (11.4%)	
Socially active	56 (17.0%)	179 (21.7%)	
Diabetes treatment, n (%)	153 (42.0%)	321 (36.7%)	0.08
Psychosocial variables			
Mean CES-D score (SD)	7.6 (6)	9.6 (6.9)	**<.001**
Depressive symptoms, n (%)	119 (36.2%)	198 (24.2%)	**<.001**
Physical health and function			
Vision impairment, n (%)	44 (12.1%)	71 (8.1%)	**0.03**
Hearing problem, n (%)	38 (10.4%)	47 (5.4%)	**0.001**
Mean body mass index (SD), kg/m2	24.9 (3.9)	24.5 (3.8)	0.13
Chair stand test	10.7 (4.2)	11.3 (4.7)	0.05
Mean walking speed (SD), meters/min	4.6 (2.4)	4.7 (2.4)	0.66
Mean grip strength (SD), kg	30.3 (10.8)	26.9 (9.5)	**<.001**

Mean IADL (SD)	4.6 (1)	4.3 (1.3)	**<.001**
Mean systolic blood pressure (SD), mmHg	134.5 (20.9)	135.6 (20.2)	0.47
Biomarkers, mean (SD)			
Cystatin C, mg/l	1 (0.3)	1 (0.3)	0.15
Blood Urea Nitrogen, mg/dl	15.7 (4.2)	16.1 (4.6)	0.13
Total Cholesterol, mg/dl	199.7 (43.2)	206.8 (48.7)	**0.02**
Creatinine, mg/dl	0.8 (0.2)	0.8 (0.2)	0.75
C-Reactive Protein, mg/l	3.6 (9)	3.5 (8)	0.98
Glucose, mg/dl	164.6 (61.9)	165.5 (73.5)	0.85
Glycated Hemoglobin, %	6.2 (1.6)	6.4 (1.7)	0.27
HDL Cholesterol, mg/dl	45.4 (16)	46 (16.5)	0.61
LDL Cholesterol, mg/dl	112.8 (40.9)	118 (39.9)	0.06
Triglycerides, mg/dl	201.6 (200.6)	212.7 (222)	0.42
Uric Acid, mg/dl	4.6 (1.3)	4.6 (1.4)	0.91
Hemoglobin, g/dl	14.6 (2.2)	14.6 (2.4)	0.93
Hematocrit	42.2 (6)	41.8 (6.2)	0.40
Cognitive function			
Mean TICS (SD)	6.9 (2.8)	6.1 (3)	**<.001**
Figure drawing, n (%)	189 (58.2%)	547 (67.8%)	**0.002**
Mean episodic memory (SD)	4 (1.5)	3.9 (1.4)	0.28
Mean total cognitive score (SD)	10.5 (4.4)	9.2 (4.6)	**<.001**

CES-D= Center for Epidemiologic Studies Depression Scale; HDL=high-density lipoprotein; LDL=low-density lipoprotein; TICS=telephone interview of cognitive status; SD=standard deviation.

Table 2. Associations between baseline potential risk factors and incidence of fall in 4 years follow-up (2011-2015) among diabetes participants of the China Health and Retirement Longitudinal Study (CHARLS).

Variables	Model 1		Model 2	
	OR (95% CI)	P	OR (95% CI)	P
Age, per 1 year	1.01 (0.99 - 1.03)	0.52	1.01 (0.98 - 1.04)	0.46
Male vs. Female	0.99 (0.61 - 1.58)	0.95	1.08 (0.61 - 1.94)	0.79
Drinking status				
Never drinker	reference	**0.03**	reference	**0.047**
Former drinker	2.22 (1.24 - 3.99)		2.32 (1.17 - 4.63)	
Current drinker	1.11 (0.69 - 1.81)		1.03 (0.57 - 1.86)	
Education groups				
No formal education or illiterate	reference	0.69	reference	0.91
Some primary school	0.79 (0.47 - 1.33)		1.25 (0.67 - 2.31)	
Finished primary school	1.02 (0.61 - 1.71)		1.19 (0.64 - 2.21)	
Junior high school or above	1.06 (0.62 - 1.81)		1.15 (0.60 - 2.20)	
Social activity				
No social activity	-		reference	**0.02**
Some social activity	-		1.42 (0.81 - 2.50)	
Socially active	-		0.53 (0.31 - 0.91)	
Diabetes treatment, Y vs. N (reference)	-		1.13 (0.75 - 1.73)	0.56
Depressive symptoms, Y vs. N (reference)	1.47 (1.03 - 2.11)	**0.03**	1.46 (0.95 - 2.26)	0.09
Having vision problem, Y vs. N (reference)	1.74 (0.97 - 3.10)	0.06	1.82 (0.92 - 3.61)	0.09
Having hearing problem, Y vs. N (reference)	0.94 (0.54 - 1.65)	0.83	0.88 (0.44 - 1.79)	0.73
BMI, per 1 kg/m2	-		0.98 (0.92 - 1.03)	0.38
Chair stand score, per unit	-		1.00 (0.96 - 1.05)	0.92
grip strength, per 5 kg	0.87 (0.79 - 0.98)	**0.02**	0.84 (0.73 - 0.96)	**0.01**
IADL, per unit	0.89 (0.75 - 1.05)	0.15	0.95 (0.77 - 1.17)	0.61
Cystatin C, per mg/l	-		0.79 (0.37 - 1.65)	0.52
Blood Urea Nitrogen, per mg/dl	-		1.06 (1.01 - 1.11)	**0.01**
Total cholesterol, per 10 mg/dL	1.04 (1.00 - 1.07)	**0.046**	1.05 (0.99 - 1.12)	0.08
Ldl Cholesterol, per mg/dl	-		1.00 (0.99 - 1.00)	0.39

TICS, per unit	1.00 (0.89 - 1.13)	0.99	1.00 (0.87 - 1.16)	0.98
Figure drawing, Y vs. N (reference)	1.12 (0.73 - 1.70)	0.60	0.95 (0.56 - 1.58)	0.83
Total cognitive score, per unit	0.96 (0.88 - 1.04)	0.34	1.00 (0.90 - 1.11)	0.94

CI=confidence interval; OR=odds ratio; TICS=telephone interview of cognitive status.

Note. Model included all variables with $p<0.05$ in univariate analyses; and model 2 included all variables with a $p<0.15$ in the univariate analyses.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-12
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Risk of falls in four years of follow-up among Chinese adults with diabetes: Findings from the China Health and Retirement Longitudinal Study

Yue Wen, Jing Liao, Yiqiong Yin, Chunjuan Liu, Renrong Gong*, Dongmei Wu*

Correspondence should be made to:

Dongmei Wu, PhD, RN

Associate professor

Department of Nursing, The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China

Huli West 1st Lane, Chengdu, Sichuan Province, China, 610036.

Tel: 86-28-69515754

E-mail: wudongmei_2001@163.com

Renrong Gong, BN, RN

Head Nurse, Department of Surgery Nursing, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041.

E-mail: gongrenrong@wchscu.cn

Tel：86-28-85421887

*: Renrong Gong and Dongmei Wu were co-corresponding authors for this manuscript.

The full names, institutions, city, and country of all other co-authors:

Yue Wen, BN, RN

Supervisor Nurse, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041.

E-mail: wenyue19820327@163.com

Jing Liao, MSN, RN, Senior Nurse, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041.

E-mail: m15982277765@163.com

Yiqiong Yin, BN, RN, Chief Superintendent Nurse, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041.

E-mail: yiqiong489@163.com

Chunjuan Liu,, Master of nursing, RN, Associate professor nurse, West China School of Nursing, Sichuan University/ West China Hospital, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041

E-mail: liuchunjuan2002@163.com

Renrong Gong, BN, RN, Head Nurse, Department of Surgery Nursing, West China Hospital, Sichuan University /West China School of Nursing, Sichuan University

37 Guoxue Xiang Street, Chengdu, China, 610041. E-mail: gongrenrong@wchscu.cn

Tel：86-28-85421887

Dongmei Wu, PhD, RN, Associate professor, Department of Nursing, The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China

Huli West 1st Lane, Chengdu, China, 610036.

Tel: 86-28-69515754.

E-mail: wudongmei_2001@163.com

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Abstract

Objectives. This study was to determine the incidence of falls and identify baseline factors increased risk for incident falls over time among people with diabetes.

Design. This study was a secondary analysis using the baseline and four years of follow-up data from the China Health and Retirement Longitudinal Study (CHARLS).

Setting. A nationally representative survey of 17,500 Chinese residents aged 45 and older were recruited in the baseline national survey in 2011. These participants were followed up every two years.

Participants. A total of 1238 middle-aged and older adults with diabetes and no history of falls at baseline were included in the current study.

Primary and secondary outcome measures. Information on incidence of falls and medical treatment resulting from falls were determined by self-report.

Results. The findings showed that the incidence of falls was 29.4% during four years of follow-up. Participants with incident falls were younger, were more likely to be women, had lower education level, and were less likely to be current drinkers. In addition, former drinkers were 2.22 times more likely to fall. Socially active individuals were 47% less likely to fall compared to those without social activities. Every 5 kg increase in grip strength was associated with a 13% lower risk of falls. A 10 mg/dL higher total cholesterol and 1 mg/dl higher blood urea nitrogen were associated with a 4% and 6% higher risk of falls. Finally, participants with depressive symptoms were 1.47 times more likely to fall compared to those without depressive symptoms.

Conclusions. These findings underscore the importance of developing a fall prevention program for those with diabetes, and this program should address potentially modifiable risk factors, including levels of total cholesterol, blood urea nitrogen, social activity, depressive symptoms, and grip strength.

Key words: incidence, falls, diabetes, middle-aged and older adults

Strengths and limitations of this study

- We used a national representative sample of participants with diabetes. Therefore, findings of our study can be generalized to adults with diabetes in China.
- Prospective associations between baseline risk factors for falls and fall events were examined in four years of follow-up.
- There might be non-differential recall bias in the current study due to using self-report of falls, which led to lower power to detect potential risk factors.
- Due to the observational nature of the study design, causal associations between these risk factors and fall events cannot be drawn from the current study.

Introduction

China is now home to the world's largest number of people with diabetes, with a report of 109.6 million adults having diabetes.[1, 2] The prevalence of diabetes increases with age, and an estimate of about 20.2% of adults over 60 years of age were diabetic in 2013.[2] Recently, emerging evidence suggests that diabetes is associated with an increased risk of falls among older adults, especially for insulin users.[3] The underlying mechanisms may lie in the diabetes-related pathological changes, which may include vestibular dysfunction, peripheral neuropathy, diabetic retinopathy, declines in muscle strength, and severe hypoglycemic events associated with insulin use.[4, 5] Falls are common in older adults with diabetes, with annual incidence rates of 39% among individuals aged 65 years or older and occurring more often in those with poor glycemic control.[6] Since falls are the leading cause of injury in older adults and can lead to decreased functional independence and lower quality of life,[7] it is critical to identify predictors that can be easily used to assess fall risks in the clinical settings among older adults with diabetes.

Recently, a few studies have examined risk factors that are associated with risk of falls among individuals with diabetes. For example, using data from the 2010 wave of the Health and Retirement Study, Blackwood[8] found that cognitive dysfunction, impairment in executive function and delayed recall, was associated with an increased risk for falls among the entire sample of older diabetes over 65 years of age and among a subsample of diabetess over 75 years of age, respectively. People receiving diabetes treatment, specially insulin users, had a significantly higher risk of falls (relatively risk=1.94) compared to non-insulin users (relative risk=1.27).[9] Other risk factors include depressive symptoms,[10] reduced physical performance (e.g., walking speed,[11] repeated chair stands,[12] and grip strength[13]), being overweight/obese,[11] and problems with instrumental activities of daily living (IADL).[14] Hypoglycemia[15] and vision impairment[16] that are associated with the disease also contribute diabetic fall risk. However, these studies were mainly cross-sectional or had limited follow-up time. Large cohort studies with longer follow-up time are needed to study factors associated with falls in older Chinese adults with diabetes. Meanwhile, associations between serum biomarkers and risk of falls are not well studied. Such prospective associations may provide valuable insights into how baseline health conditions may predict risk of falls in the follow-up periods and help develop effective strategies to address these risk factors during primary health care service. Therefore, the purpose of this study was to determine the incidence of falls and examine a comprehensive list of potential risk factors associated with falls in four years of follow-up among participants with diabetes of the China Health and Retirement Longitudinal Study (CHARLS).

Methods

Study Design

This was a secondary data analysis of prospective data from the CHARLS. The CHARLS is an ongoing, biannual national survey, sponsored by the National Natural Science Foundation of China, the National Institute on Aging, and the World Bank.[17] The CHARLS questionnaire collects a substantial data on an individual's sociodemographic information, family structure, biomarkers, health status, physical performance, health insurance, employment history, retirement and pension, individual and household assets, and community level information.[17] Participants were selected using a multistage, stratified, cluster probability sampling strategy.[18] The sampling strategy has been previously described in detail,[19] and the study data sets can be downloaded at the CHARLS home page at http://charls.pku.edu.cn/en. A representative sample of 17,314 community-dwelling individuals of 45 years or older across the country was recruited

into the baseline wave of CHARLS, which was fielded in 2011 to 2012. The current analysis used data from baseline, the first, and the second follow-up surveys.

Study Sample

CHARLS participants with diabetes who had no history of falls and had complete data on age, gender, education level, falls, cognitive measures, body weight, height, walking speed, standing balance test, depressive symptoms, diabetes treatment, and plasma biomarkers at the time of the baseline survey were included in the current study. The final sample included in this study consisted of 1238 Chinese adults with diabetes.

The American Diabetes Association[20] criteria was used to define diabetes status. Specifically, participants were diagnosed with diabetes if self-reporting to take hypoglycemic agents (i.e., insulin use, or taking oral hypoglycemic medications including traditional Chinese, modern western medicine, or other diabetes treatment), fasting blood glucose ⩾126 mg/dL, or random blood glucose ⩾200 mg/dL, or HbA1c ⩾6.5%. Fasting venous blood samples were collected by trained health professionals on the day of physical examination. However, a small proportion (8%) of participants did not fast.[21] For those participants, random blood glucose and/or HbA1c were used to define diabetes.

Patient and Public Involvement

In the current study, we used de-identified data from the CHARLS with no direct involvement of or interaction with participants in the design, recruitment or conduct of the original cohort study.

Variables, Definitions, and Measures

Falls. Information on incidence of falls and medical treatment resulting from falls was collected in the CHARLS. The participant was asked if he/she had fallen down in the past two

years prior to the survey. If the participant answered "yes" to this question, he or she was then asked to indicate how many times falls resulted in a medical treatment.

Measurement of potential risk factors. Potential risk factors included demographics, lifestyle behaviors, depressive symptoms, physical health and functioning variables, biomarkers, cognitive function, and diabetes treatment. Demographics and lifestyle behaviors were measured based on self-report. Information on age, gender, marital status, and education levels was collected using face-to-face interviews. Marital status was categorized as married or separated. Education levels included no formal education/illiterate, some primary school, finish primary school, and junior high school or above. Lifestyle behaviors included smoking, drinking, and social activities. Smoking and drinking status were categorized as never, former and current users. Social activity was measured as no social activity, some social activity, and socially active.

Depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale (CES-D) short form.[22] The CES-D short form consists of ten items, and each item is rated on a four-point Likert scale ranging from 0 (rarely or none of the time) to 3 (most or all of the time) with a total possible summary score of 0 to 30.[22] Two positive symptoms (i.e., "was happy" and "hopeful about the future") were reversely coded before data analysis. The time frame refers to the week prior to the participants' interview date. The CES-D short form has been validated among a subsample of 742 CHARLS participants aged 60 years and older and has shown adequate psychometric properties. A CES-D score of 12 or higher was defined as having major depressive symptoms.[23]

Physical health and functioning variable included vision and hearing function, body mass index (BMI), repeated chair stand test, walking speed, grip strength, systolic blood pressure (SBP), and IADL. Vision and hearing impairments were self-reported by study participants. BMI

was calculated by dividing body weight in kilograms by the square of body height in meters, kg/m^2. To conduct repeated chair stand test, participants were asked to sit in the middle of the chair and place their hands on the opposite shoulder. Then they were asked to rise to a full standing position and sit back down again for five times. The examiner recorded the time if the participants finished the test without arms. If the participants must use their arms to stand, the examiner stopped the test, and recorded "0" for the number and score. The median time of five tests was used in the analysis. All participants aged 60 years or older without physical limitations that may interfere with walking were eligible for the test of walking speed. Participants were instructed to walk on a straight 2.5-meter flat course twice (there and back) at their normal walking speed. The examiner used a stopwatch to record the elapsed time necessary to walk the distance. The median time of the two tests was used as a measure of walking speed.[24, 25] A hand-held dynamometer was used to assess grip strength. Participants were instructed to squeeze the dynamometer with all of their strength for a few seconds, typically twice with each hand, and alternate hands between tests. Consistent with a prior CHARLS publication,[26] an average score was calculated using the four measurements from both hands. IADL refers to meal preparation, doing housework, shopping, managing personal finances, and managing medications, and these activities were measured with scores ranging from 0 to 5.[27] Higher scores indicate having more difficulty in performing IADL, and loss of independence and mobility.

Biomarkers included blood lipids (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides), blood glucose (fasting glucose and hemoglobin A1c), creatinine, cystatin C, uric acid, blood urea nitrogen, C-reactive protein, hemoglobin, and hematocrit.

Subdomains of cognition measured in the CHARLS included visuospatial abilities, episodic memory, and orientation/attention. Consistent with prior CHARLS publications,[24, 25] an overall cognitive score was calculated as a sum of these three cognitive subdomains, which could range from 0 to 21 and was used to indicate overall cognitive functioning of the participant.

Figure drawing. As previously presented by CHARLS,[24, 25] the examiner first demonstrated a picture of two overlapping pentagons and the participant was required to draw a similar picture. Those who correctly drew the picture received a score of 1, while those who failed to draw the picture received a score of 0. This test was designed to measure a person's capacity to identify visual and spatial relationships among objects.

Word recall. This was a memory task for assessing both immediate and delayed recall. The immediate recall test involved presenting the participant with a list of 10 random words, which were read at a constant rate of 1 word every 2 seconds. At the end of the presentation, the participant was given up to 2 minutes to recall the list of words. Approximately 4 to 10 minutes later, a delayed recall test was administered by asking the participant to recall the list of 10 words presented earlier. For each task, the number of correctly recalled words was scored, with higher scores indicating better memory performance. In line with prior CHARLS publications,[24, 25] an episodic memory score could range from 0 to 10 by averaging number of correctly recalled words from both immediate and delayed word tasks.

The Telephone Interview of Cognitive Status (TICS-10). The original TICS is a global mental status test that can either be administered over the telephone or face-to-face.[28] As previously presented by CHARLS,[24, 25] ten questions from the original TICS were used in the CHARLS baseline survey, including date (day, month, and year), day of the week, the serial subtraction of 7 beginning with the number 100 up to five times, and season of the year. The

TICS-10 was used to assess orientation/attention, and it was calculated as the sum of correct answers which could range from 0 to 10.[29]

Treatment of diabetes was based on self-report. Participants were asked whether they took medications, including traditional Chinese medicine, modern medicine, and insulin, to treat diabetes. Participants that took any of the medications were coded as receiving anti-diabetic treatment.

Ethical Considerations

The CHARLS was approved by the Peking University Ethical Review Committee. All participants provided signed written consent forms in the original CHARLS study.[21]
The current study is a secondary analysis of the de-identified CHARLS public data. The Ethics Review Committee at University of Electronic Science and Technology of China granted an exempt research determination to the current study.

Statistical Analysis

Baseline characteristics of the participants were summarized as mean and standard deviation or median and interquartile range for continuous variables and frequency and percentage for categorical variables. Binary associations between incidence of falls and potential risk factors at baseline were tested using Chi-squared tests for categorical variables and one-way analyses of variance (ANOVA) for continuous variables. Significant variables in the binary analyses were added in a multivariable logistic regression model to identify risk factors for fall. Odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were reported. In a sensitivity analysis, we also include variables with a p value <0.15 into the full model. The SAS 9.4 (SAS Institute Inc., Cary, North Carolina) was used to analyze the data. All p values were two-sided, and p<0.05 was considered significant.

Results

Characteristics of the Study Participants

A total of 1,238 participants with diabetes who reported no falls in the 2011 baseline visit were included in the current analyses, of whom, 364 (29.4%) reported to have fall(s) in 4 years of follow-up. As shown in Table 1, compared to participants had no incident fall, those with incident falls were younger (59.4 vs. 61.8), were more likely to be women (56.9% vs. 49.0%), had lower education level (illiterate rate: 33.2% vs. 24.9%), and were less likely to be current drinkers (13.8% vs. 21.6%). In addition, participants having incident fall(s) were more likely to be socially inactive (68.2% vs. 67.0%) and receive diabetes treatment (42.0% vs. 36.7%). However, these differences were not statistically significant (P=0.09 and 0.08 respectively). The two group of participants were similar in living areas, marital status, and smoking status.

Significant Variables in Bi-variable Analyses

In addition to age, gender, education level, and drinking status as described above, depressive symptoms, vision impairment, hearing problem, grip strength, IADL, total cholesterol, TICS-10, figure drawing, and total cognitive scores were also significantly associated with incident falls in the bi-variable analyses (Table 1).

Full-Model Results

As shown in Table 2, when putting all significant variables identified in the bi-variable analyses in the full model, only drinking status, grip strength, total cholesterol, and depressive symptoms were significant predictors of incident fall(s). Vision impairment was a nominally significant predictor. Compared to never drinkers, former drinkers were 2.22 times (95% CI:

1.24 – 3.99) more likely to fall. However, current drinker had a similar risk as never drinkers (OR=1.11, 95% CI: 0.69 – 1.81). Every 5 kg increase in grip strength was associated with a 13% (95% CI: 2% - 21%) lower risk of falls. A 10 mg/dL higher total cholesterol was associated with a 4% (95% CI: 0% - 7%) higher risk of falls. Finally, participants with depressive symptoms were 1.47 (95% CI: 1.03-2.11) times more likely to fall compared to those without depressive symptoms.

Furthermore, when adding all variables with a p<0.15 in the bi-variable analyses, p values for depressive symptoms (P=0.09) and total cholesterol (P=0.08) became nominally significant, however magnitudes of the associations did not change much. Furthermore, two new variables, social activity and blood urea nitrogen were significantly associated with risk of fall. Compared to people with no social activity, socially active individuals were 0.53 (95% CI: 0.31 – 0.91) times less likely to have fall. On contrary, one mg/dl higher blood urea nitrogen (BUN) was associated with 1.06 (95% CI: 1.01 - 1.11) times higher risk for fall.

Discussion

In this prospective analysis among this nationally representative sample of middle-aged and older Chinese diabetes participants without any history of fall(s), 29.4% reported to have incidence of falls in 4 years of follow-up. Compared to participants had no incident fall, those with incident falls were younger, were more likely to be women, had lower education attainment, and were less likely to be current drinkers. Furthermore, we identified four factors predicting risk for falls, including drinking status, grip strength, total cholesterol, and depressive symptoms. These findings will not only benefit allocation of health care resources to address health conditions, but also provide evidence for prevention strategies of falls in this population.

Alcohol consumption has been considered as a risk factor for falls by the World Health Organization, as physiological changes related to aging may increase sensitivity to alcohol use in older adults.[30] However, few studies have examined alcohol use as a risk for falls in community-dwelling older adults with diabetes. In this study, we found that former drinkers had a more than twice the risk of falls compared to never drinkers, however current drinkers had a similar risk as never drinkers. The findings are consistent with a previous study; in a large-scale study among 289,187 adults in the 2004-2013 U.S. National Health Interview Surveys, former drinker had a similar higher risk of falls as at-risk drinkers, compared to lifetime abstainers.[31] A possible reason could be that former drinkers might have stopped drinking due to poor health status which predisposed them to risk of fall. In the current study, compared to never drinkers, former drinkers were more likely to have vision impairment and take diabetes medications. It is possible that the vision impairment was due to worse glucose control, and former drinkers were highly suggested by doctors to take diabetes medications. Future studies with larger sample sizes, particularly for former drinkers, and more detailed measures of health status are warranted to further validate our findings. Nevertheless, studies have shown that low-to-moderate drinking was associated with a reduced risk of fall.[32] In the CHARLS, about two thirds of the current drinkers were moderate drinkers (defined as having ≤14 drinks per week), and the remaining were at-risk drinkers (defined as having >14 drinks per week).[33] In the current study, current drinkers had a similar risk of fall as never drinkers. This may be a result of mixture of moderate and at-risk drinking. However, these are preliminary findings that need to be better investigated in future studies.

The hand grip strength is an indicator of muscle strength, which is important to fall prevention.[34] Grip strength was negatively associated with risk of falls in the current study, and this finding is intuitive and consistent with previous studies, which have repeatedly demonstrated a negative association between stronger grip strength and reduced fall events.[13, 35-37] Our study provided further evidence that stronger grip strength at baseline was longitudinally associated with a less risk of falls in four-year follow-up among an older population with diabetes in China. In addition, hand grip strength has also been linked to other important diabetes outcomes. Using longitudinal data from the UK Biobank, Celis-Morales et al.[38] found that patients with diabetes who had stronger grips had a reduced risk of all-cause mortality, lower risk of death from cardiovascular disease mortality, and less risk of developing cardiovascular disease. However, a decline in hand grip strength has been reported among individuals with diabetes compared to healthy individuals.[39] Taken together, these studies suggest that reduced grip strength may be used to identify a subgroup of patients with diabetes who are at a higher risk of falls and other important diabetes outcomes, and it is important to develop strategies to increase hand grip strength in this population.

Higher total cholesterol and BUN levels at baseline increased the risk of falls at follow-up in the current study. Previous studies that examined the relationship between biomarkers and fall risks have primarily focused on levels of high-density lipoprotein cholesterol,[40] which were not associated with fall events in the current study. Levels of total cholesterol are inversely associated with plasma 25-hydroxyvitamin D levels,[41] which are an important marker for frailty among Chinese community-dwelling older adults.[42] Levels of total cholesterol are also inversely associated with lean body mass,[43] which is important to determine risks of falls in older Asian adults.[44] However, plasma 25-hydroxyvitamin D and lean body mass were not measured in the CHARLS, so we were not able to examine whether these two biomarkers may explain the association between levels of total cholesterol and fall events in this study. Since grip strength is correlated with lean body mass, we tried to evaluate total cholesterol and fall associations before and after controlling for grip strength, however, adding grip strength only slightly changed the effect of total cholesterol on fall. BUN reflects fluid depletion and is also influenced by protein intake, catabolism and tubular reabsorption.[45, 46] Dehydration is an important risk factor for fall and water intake could significantly reduce risk for fall in nursing homes.[47] However, in a case-control study among hospitalized patients, BUN was not associated fall.[46] Our study provided longitudinal evidence among a community dwelling older adults that higher BUN is associated with high risk for fall. Future studies of more biomarkers, such as metabolomics studies, may identify additional biomarkers and reveal underlying mechanisms of falls in this population.

The current study found that higher depressive symptoms may predict falls over time among individuals with diabetes. Such association has been widely reported in case-control, cross-sectional, and short-term prospective studies in the general populations.[48-51] Our study added further evidence with a larger sample size and a longer follow-up time among individuals with diabetes. Evidence suggested that baseline depressive symptoms increased fall risks through at least three different mechanisms. First, overall antidepressant use, particularly tricyclic antidepressants, are considered to contribute to falls because they increase sedation and risk of orthostatic hypotension.[52] Second, compared to the general population, patients with diabetes are more likely to experience depression.[53] A meta-analysis[54] demonstrated a significant association between depression and treatment non-adherence, including failing to engage in regular exercise among individuals with diabetes. As regular exercise contributes to muscle strength,[55] those who do not exercise regularly may have weaker muscle strength, which is associated with an increased risk of falls at follow-up. Third, depression and falls are also linked with each other through several common risk factors. Fear of falling, functional decline, history of falls, and cognitive dysfunction have been separately linked to both depression and falls.[49] However, due to social discrimination, depression was not routinely screened in clinical practice in China. Only a small proportion of patients with depressive symptoms (5-8%) were diagnosed with depression, and less than half of patients who were diagnosed with depression sought care over time.[56, 57] Our study highlighted the importance of screening depression to prevent fall among patients with diabetes in China.

Socially active individuals also had lower risk of fall in the current study. This finding is consistent with previous studies, in which, social engagement could improve physical and mental health and reduce risk of fall.[58-61] In the current study, even after adjusting for physical and cognitive function measures, social activity was still associated with lower risk of fall. As hypothesized in previous studies, for socially active individuals, attention to environmental hazards and adaptation to changes in physical function may be triggered and encouraged by peers in social activities. Furthermore, socially active individuals may be more likely to get assistance from peers in routine or occasional tasks, such as reaching to an object on a high shelf during shopping.[58]

The findings of the current study have important implications for clinical practice. Given the high incidence of fall events (29.4%) among middle-aged and older adults with diabetes, it is important to develop a screening program with the goal of identifying at-risk and ensuring these individuals receive fall prevention programs. The identified risk factors, including drinking status, hand grips strength, blood lipids, and depressive symptoms, should be integrated into the screening program. In addition, as symptoms of depression are a potentially modifiable risk factor for falls, they should be addressed in fall prevention programs. Treatment of depressive symptoms by non-pharmacological approaches, such as physical exercise or psychosocial therapies such as mindfulness, should be considered as part of fall prevention programs in this high-risk population for falls.[62] Interventions to reduce the likelihood of falls among individuals with diabetes who have weak grip strength should focus on a combination of physical exercise, including resistance[55] and aerobic training exercises,[63] which has been shown to improve grip strength in patients with diabetes. Fall prevention programs should also target reducing levels of total cholesterol, as these individuals were at a higher risk of falls. Participants should be advised to first make lifestyle changes to improve cholesterol, including diet changes and increasing physical activity.

This study has several important strengths. A major strength of our study is that we used a national representative sample of participants with diabetes. Therefore, findings of our study can be generalized to persons with diabetes in China. In addition, we have also evaluated a comprehensive list of risk factors to predict fall events in 4 years of follow-up. Previous studies of falls have focused on limited number of factors.[8-16] Furthermore, a prospective cohort design was used, which avoided temporal ambiguity of potential factors and falls, and reduced survival bias, in which, an identified factor may be a result of fall rather than a risk factor. Finally, to ensure data integrity and validity, quality assurance measures have been implemented throughout the process of data collection in the CHARLS. These measures include reviewing data collection forms for completeness and accuracy of the data, verifying accuracy of data in electronic databases, as well as calling back participants.[18]

Our study also has limitations that need to be acknowledged. As in all population-based studies, fall events were determined by self-report. Previous research consistently showed that older adults tended to underreport falls because they did not recognize the severity of a fall or did not remember a fall with less severe consequences.[64] Therefore, there might be recall bias, and we should expect that the fall events may be underreported by participants in the current study. A prospective design with "daily fall calendar" is considered the golden standard to measure fall events,[64] and this method should be incorporated into future studies to more accurately capture fall events among individuals with diabetes. Another limitation of the study is that information on number of glucose-lowering medications was not collected. Therefore, we could not assess whether number of medications may be a risk factor for fall risks in this population. Furthermore, some important and widely acknowledged risk factors, such as diabetic neuropathy and autonomic neuropathy were not measured in the CHARLS. We were not able to assess their contributions to fall in this population. Finally, this study examined the prospective relationships of baseline risk factors for falls with fall events in four-year follow-up, and therefore no causal associations between these risk factors and fall events can be drawn from the current study.

Conclusions

To conclude, through a longitudinal study among a nationally representative sample of middle-aged and older participants with diabetes, we estimated that the incidence of fall events in 4 years of follow-up was as high as 29.4%. We also identified four factors predicting fall events. Besides the five risk factors (i.e., alcohol drinking, grip strength, social activity, depressive symptoms, and BUN), that have been reported in previous case-control, cross-sectional, and/or short-term prospective studies, our study identified a novel risk factor (i.e., levels of total cholesterol) to predict fall events among individuals with diabetes. Future studies of more biomarkers, such as a metabolomics study, are warranted to identify additional biomarkers for and reveal underlying mechanisms of fall events among this vulnerable population.

Contributorship Statement

All authors contribute to the conception and design of this study. YW, JL, CL, and DW were responsible for the design, analysis, drafting and revision of this manuscript. RG and YY were responsible for interpretation of data and preparation of the manuscript.

Competing Interests Statement

None declared.

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Patient Consent for Publication

Not required.

Data Sharing Statement

The study used a public data from the CHARLS that were obtained from the CHARLS home page at http://charls.pku.edu.cn/en.

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Tables

Table 1. Baseline characteristics of diabetic participants of the China Health and Retirement Longitudinal Study (CHARLS) according to incidence of fall in 4 years follow-up (2011-2015).

Variable	Incident Fall (n=364)	No Fall (n=874)	*P*
Demographics			
Age	59.4 (9.3)	61.8 (9)	**<.001**
Male, n (%)	157 (43.1%)	446 (51.0%)	**0.01**
Rural, n (%)	278 (76.4%)	655 (74.9%)	0.59
Married, n (%)	316 (86.8%)	784 (89.6%)	0.16
Education groups, n (%)			**0.02**
No formal education/illiterate	120 (33.2%)	218 (24.9%)	
Some primary school	61 (16.9%)	161 (18.4%)	
Finish primary school	78 (21.6%)	193 (22.1%)	
Junior high school or above	102 (28.3%)	302 (34.6%)	
Lifestyle behaviors			
Smoking, n (%)			0.41
Nonsmokers	230 (63.5%)	523 (59.9%)	
Former Smokers	45 (12.4%)	109 (12.5%)	
Current Smokers	87 (24.0%)	241 (27.6%)	
Drinking status, n (%)			**0.01**
Never	258 (75.7%)	592 (71.3%)	
Former	36 (10.6%)	59 (7.1%)	
Current	47 (13.8%)	179 (21.6%)	
Social activities, n (%)			0.09
No social activity	225 (68.2%)	553 (67.0%)	
Some social activity	49 (14.9%)	94 (11.4%)	
Socially active	56 (17.0%)	179 (21.7%)	
Diabetes treatment, n (%)	153 (42.0%)	321 (36.7%)	0.08
Psychosocial variables			
Mean CES-D score (SD)	7.6 (6)	9.6 (6.9)	**<.001**
Depressive symptoms, n (%)	119 (36.2%)	198 (24.2%)	**<.001**
Physical health and function			
Vision impairment, n (%)	44 (12.1%)	71 (8.1%)	**0.03**
Hearing problem, n (%)	38 (10.4%)	47 (5.4%)	**0.001**
Mean body mass index (SD), kg/m2	24.9 (3.9)	24.5 (3.8)	0.13
Chair stand test	10.7 (4.2)	11.3 (4.7)	0.05
Mean walking speed (SD), meters/min	4.6 (2.4)	4.7 (2.4)	0.66
Mean grip strength (SD), kg	30.3 (10.8)	26.9 (9.5)	**<.001**

Mean IADL (SD)	4.6 (1)	4.3 (1.3)	**<.001**
Mean systolic blood pressure (SD), mmHg	134.5 (20.9)	135.6 (20.2)	0.47
Biomarkers, mean (SD)			
Cystatin C, mg/l	1 (0.3)	1 (0.3)	0.15
Blood Urea Nitrogen, mg/dl	15.7 (4.2)	16.1 (4.6)	0.13
Total Cholesterol, mg/dl	199.7 (43.2)	206.8 (48.7)	**0.02**
Creatinine, mg/dl	0.8 (0.2)	0.8 (0.2)	0.75
C-Reactive Protein, mg/l	3.6 (9)	3.5 (8)	0.98
Glucose, mg/dl	164.6 (61.9)	165.5 (73.5)	0.85
Glycated Hemoglobin, %	6.2 (1.6)	6.4 (1.7)	0.27
HDL Cholesterol, mg/dl	45.4 (16)	46 (16.5)	0.61
LDL Cholesterol, mg/dl	112.8 (40.9)	118 (39.9)	0.06
Triglycerides, mg/dl	201.6 (200.6)	212.7 (222)	0.42
Uric Acid, mg/dl	4.6 (1.3)	4.6 (1.4)	0.91
Hemoglobin, g/dl	14.6 (2.2)	14.6 (2.4)	0.93
Hematocrit	42.2 (6)	41.8 (6.2)	0.40
Cognitive function			
Mean TICS (SD)	6.9 (2.8)	6.1 (3)	**<.001**
Figure drawing, n (%)	189 (58.2%)	547 (67.8%)	**0.002**
Mean episodic memory (SD)	4 (1.5)	3.9 (1.4)	0.28
Mean total cognitive score (SD)	10.5 (4.4)	9.2 (4.6)	**<.001**

CES-D= Center for Epidemiologic Studies Depression Scale; HDL=high-density lipoprotein; LDL=low-density lipoprotein; TICS=telephone interview of cognitive status; SD=standard deviation.

Table 2. Associations between baseline potential risk factors and incidence of fall in 4 years follow-up (2011-2015) among diabetes participants of the China Health and Retirement Longitudinal Study (CHARLS).

Variables	Model 1		Model 2	
	OR (95% CI)	P	OR (95% CI)	P
Age, per 1 year	1.01 (0.99 - 1.03)	0.52	1.01 (0.98 - 1.04)	0.46
Male vs. Female	0.99 (0.61 - 1.58)	0.95	1.08 (0.61 - 1.94)	0.79
Drinking status				
Never drinker	reference	**0.03**	reference	**0.047**
Former drinker	2.22 (1.24 - 3.99)		2.32 (1.17 - 4.63)	
Current drinker	1.11 (0.69 - 1.81)		1.03 (0.57 - 1.86)	
Education groups				
No formal education or illiterate	reference	0.69	reference	0.91
Some primary school	0.79 (0.47 - 1.33)		1.25 (0.67 - 2.31)	
Finished primary school	1.02 (0.61 - 1.71)		1.19 (0.64 - 2.21)	
Junior high school or above	1.06 (0.62 - 1.81)		1.15 (0.60 - 2.20)	
Social activity				
No social activity	-		reference	**0.02**
Some social activity	-		1.42 (0.81 - 2.50)	
Socially active	-		0.53 (0.31 - 0.91)	
Diabetes treatment, Y vs. N (reference)	-		1.13 (0.75 - 1.73)	0.56
Depressive symptoms, Y vs. N (reference)	1.47 (1.03 - 2.11)	**0.03**	1.46 (0.95 - 2.26)	0.09
Having vision problem, Y vs. N (reference)	1.74 (0.97 - 3.10)	0.06	1.82 (0.92 - 3.61)	0.09
Having hearing problem, Y vs. N (reference)	0.94 (0.54 - 1.65)	0.83	0.88 (0.44 - 1.79)	0.73
BMI, per 1 kg/m2	-		0.98 (0.92 - 1.03)	0.38
Chair stand score, per unit	-		1.00 (0.96 - 1.05)	0.92
grip strength, per 5 kg	0.87 (0.79 - 0.98)	**0.02**	0.84 (0.73 - 0.96)	**0.01**
IADL, per unit	0.89 (0.75 - 1.05)	0.15	0.95 (0.77 - 1.17)	0.61
Cystatin C, per mg/l	-		0.79 (0.37 - 1.65)	0.52
Blood Urea Nitrogen, per mg/dl	-		1.06 (1.01 - 1.11)	**0.01**
Total cholesterol, per 10 mg/dL	1.04 (1.00 - 1.07)	**0.046**	1.05 (0.99 - 1.12)	0.08
Ldl Cholesterol, per mg/dl	-		1.00 (0.99 - 1.00)	0.39

TICS, per unit	1.00 (0.89 - 1.13)	0.99	1.00 (0.87 - 1.16)	0.98
Figure drawing, Y vs. N (reference)	1.12 (0.73 - 1.70)	0.60	0.95 (0.56 - 1.58)	0.83
Total cognitive score, per unit	0.96 (0.88 - 1.04)	0.34	1.00 (0.90 - 1.11)	0.94

CI=confidence interval; OR=odds ratio; TICS=telephone interview of cognitive status.

Note. Model included all variables with $p<0.05$ in univariate analyses; and model 2 included all variables with a $p<0.15$ in the univariate analyses.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-12
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	13
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	14
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.