

The association of multimorbidity of metabolic syndrome and depression on type 2 diabetes: A general population cohort study in Southwest China

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Abstract

Background

Metabolic syndrome (MetS) and depression are independently associated with type 2 diabetes (T2DM) risk. However, little is known about the combined effect of MetS and depression on the risk of T2DM. The present study aims to prospectively explore the effect of MetS together with depression on T2DM susceptibility among Chinese general population.

Methods

6489 general population without T2DM of adults in Southwest China were recruited from 2010 to 2012. Depression and MetS were prospectively assessed by using 9-item Patient Health Questionnaire and Chinese guidelines for the prevention and treatment of type 2 diabetes during 2017–2020, respectively. Modified Poisson regression models were conducted to estimate risk ratio and 95% confidence intervals for independent and combined associations of MetS and depression with incidence of T2DM.

Results

During a median follow-up of 7.4 years, 678 cases of T2DM were documented. Individuals with MetS were 1.03–1.71 times more likely to develop T2DM compared with those without MetS. The corresponding RR for depression with no depression was 1.22–1.72. Notably, compared with no MetS and depression, the multivariate-adjusted RR for combined effect of MetS and depression on risk of T2DM was 2.11 (1.39–3.22). Moreover, an increased risk of T2DM were more apparent in those who were over 60 years, males, and overweight population.

Conclusions

Individuals with multimorbidity of MetS and depression are at a higher risk of T2DM compared with those who with no MetS and depression.

Introduction

Diabetes mellitus (DM) is one of worldwide well-recognized and uncontrollable common metabolic diseases with a 9.3% (463 million) of the global prevalence [1], among 90% of which is type 2 diabetes mellitus (T2DM) [2]. The highest number of T2DM exist in China, which was reported to affect 116 million humans [3]. Hence, T2DM posed a serious threat and heavy economic burden to the health of the Chinese population [4]. Regrettably, identified physical inactivity, genetic susceptibility, and diet habit fail to effectively and fully explain the etiology of T2DM. Importantly, the complex interaction regarding different pathogenic factors also plays significant role in the etiology of T2DM, which may present another

perspective for uncovering the initiation of T2DM[5]. Given that mental illness[6] and metabolic disorder[7, 8] are both closely associated with[9–12] the risk of T2DM. Therefore, combined disorder of psychological disorders and metabolic disorder is likely to have a potential effect on occurrence of T2DM.

Actually, individuals often suffer from multiple chronic diseases at the same time, which is called multimorbidity. It is defined as the existence of two or more chronic diseases[13]. The prevalence of multimorbidity is continuously increasing which generate adverse threat for human health. Therefore, it is meaningful to dissect the complex etiology of chronic non-communicable diseases from the perspective of multimorbidity. MetS, a pathological condition including insulin resistance, abdominal obesity, hyperlipidemia, and hypertension[14], affecting 20–25% of the adults worldwide[15]. MetS has been shown to be consistently and independently associated with an increased risk of DM, especially for T2DM among general population settings. Emerging evidence indicated that depression, another crucial healthcare burden, contributes to increased mortality[16] and a panel of serious metabolic complications [17]. Interestingly, population suffer from depression and antidepressants were all are more prone to T2DM [18].

Evidences indicate that there is an inner link exist between depression and MetS[19, 20]. Importantly, the above notion was strengthened by the evidence that depression is a pathogenic factor for MetS[21]. Moreover, insulin resistance commonly along with the occurrence of depression and implicates the progression of depression[22]. In fact, the two diseases often cluster in pairs and closely interact with each other. However, the combined effect of these risk markers on the risk of T2DM is still remains unknown. Ample evidences have indicated that many diseases or pathological status could synergistically promote the incidence of T2DM. A study found that the cumulative effect of obesity and MetS significantly links to raised incidence of T2DM[23]. Furthermore, patients with depressive symptoms and poor sleep quality had lower T2DM-related quality of life compared with who have depression or poor sleep quality[24]. In addition, insulin resistance is a common important characteristic of both depression and MetS, and also functions as one key pathogenesis of T2DM[25]. Thus, it is seemed to be a synergistic interaction between depression and MetS, and other T2DM-related risk factor to boost increased T2DM risk. In view of the closed association of both MetS and depression with pathogenesis of T2DM, we hypothesized that Mets and depression could synergistically associated with T2DM in the general population. Therefore, we evaluated the combined association of MetS and depression with the risk of T2DM based on Guizhou natural population cohort study. Our results could provide scientific evidence for preventing T2DM incidence for the population with multimorbidity of metabolic disease and mental disorders.

Methods

Study population

The Guizhou natural population cohort study comprised a representative sample of 9280 participants aged ≥ 18 years. The participants were recruited using multistage proportional stratified cluster sampling from 48 townships in 12 districts of Guizhou province between October 2010 and August 2012. In the present study, the average follow-up time was 7.4 years, and 8165 participants have completed at least one follow-up. We excluded participants who have diagnosed with T2DM at baseline ($n = 530$), missing outcome of T2DM at the follow up ($n = 88$), and missing or wrong data at baseline ($n = 1058$) (Fig. 1). After the above careful screening, there were 6489 remaining participants who were eligible for our study. We obtained the approval of institutional Review Committee of Guizhou Center for Disease Control and Prevention (No.S2017-02) for the implement of this study. And, all participants signed written informed consent.

Measurement of blood biochemistry markers and lifestyle

Participants were instructed to fast overnight at least 12 h prior to blood specimen collections. Triglycerides (TG) and high density lipoprotein cholesterol (HDL-C) were measured by trained professionals with qualified central laboratory. Additionally, participants were given 75 g of glucose to perform a 2-h oral glucose tolerance test (OGTT) to test fasting blood glucose (FPG) and 2-hour postprandial blood glucose (2h PG). The assessment of sociodemographic factors (age, sex, region, education level and marital status), anthropometric measures (weight and height), medication history and family history of diseases (T2DM, hypertension), behavioural risk factors (smoking and alcohol consumption), dietary intakes (The daily intake of oil and salt was calculated by asking 'how many kilos of oil/salt do you usually consume in a month' through inquiry), level of physical activity, mental health and death information were obtained via face-to-face interviews. Blood pressure was documented with the average value of three repeated measurements using the same model electronic sphygmomanometer. Hypertension was defined by the JNC 7 [26] as follows: (1) self-reported hypertension or use of hypertension medications; and/or (2) systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg.

Ascertainment of outcomes

T2DM was the endpoint of the study. The T2DM patients who were determined as T2DM was according to self-reported physician diagnosed diabetes or use of hypoglycemic agents or blood glucose examinations. The diagnostic criteria of the American Diabetes Association (ADA, 2019), T2DM is defined as: 1) a self-reported previous diagnosis by health professionals, or 2) fasting blood glucose ≥ 7.0 mmol/L (126 mg/dL), or 3) 2-hour blood glucose ≥ 11.1 mmol/L (200 mg/dL), or 4) HbA1c concentration $\geq 6.5\%$.

Assessment of depression and MetS

item Patient Health Questionnaire (PHQ-9), a brief self-assessment of depressive symptoms with high accuracy, reliability, and validity [27, 28], and has been verified by structured diagnostic interviews conducted by mental health professionals [29], which has been widely used to define depression. Participants rate nine depressive symptoms and their frequency/ duration over the previous two weeks.

PHQ-9 is computed by summing the scores of 9 symptom items (range, 0–27). In our study, the subjects who were diagnosed as depression according to PHQ ≥ 5 points.

MetS was assessed according to the Chinese guidelines for the prevention and treatment of type 2 diabetes (CDS2020), the diagnostic criteria of MetS are as follows: Abdominal obesity: male waist circumference ≥ 90 cm, female waist circumference ≥ 85 cm; Hyperglycemia: fasting blood glucose ≥ 6.1 mmol/L or 2-hour postprandial blood glucose ≥ 7.8 mmol/L and/or diabetes has been diagnosed and treated; Hypertension: blood pressure $\geq 130/85$ mmHg and/or hypertension has been confirmed and treated; Fasting triglyceride ≥ 1.70 mmol/L; Fasting HDL-C < 1.04 mmol/L. Adult Treatment Panel III (ATP 2005) [30] for MetS in sensitivity analysis: (1) Asian male waist ≥ 90 cm, Asian female waist ≥ 80 cm; (2) TG ≥ 1.7 mmol/L, or have received corresponding treatment; (3) Male HDL-C < 1.03 mmol/L, female HDL-C < 1.29 mmol/L, or have received corresponding treatment; (4) Blood pressure $\geq 130/85$ mmHg and/or have been diagnosed hypertension and receive corresponding treatment; (5) FPG ≥ 5.6 mmol/L, or those who have been diagnosed T2DM and treated. Those who meet 3 items or more can be diagnosed MetS based on CDS2020 and ATP, respectively.

Covariates

The covariates which were adjusted in regression models were based on previous studies regarding the relationship of MetS or depression with T2DM and the potential biological mechanisms. Covariates listed in our study including age, sex(male, female), region(urban or rural), nation(the Han nationality or other), marital status(married or other), and education level(no formal school, primary, middle school, high school, college/university or more), smoking status(everyday, sometime or never), excessive drinking status(yes or no), physical activity(never, 1–2 days per week, ≥ 3 days per week), oil intake(≥ 25 g/d or < 25 g/d), salt intake(≥ 6 g/d or < 6 g/d), family history of diabetes(yes or no), and body mass index (BMI). BMI was measured by weight/height² (kg/m²).

Statistical Analysis

To investigate the joint associations of MetS and depression with incidence of T2DM, participants were classified into four categories of no depression and MetS, depression only, MetS only, MetS together with depression and who with no MetS and depression were used as a reference group. Continuous numerical variables are described by mean \pm standard deviation ($\bar{X} \pm SD$), and classified variables are expressed in the form of n (%). The statistical differences among the four groups at baseline were analyzed by one-way ANOVA, Kruskal Wallis or chi square test as appropriate. Modified Poisson regression model was used to examine independent and synergistical association of MetS and depression with T2DM by calculating relative risk (RR) and 95% confidence interval (CI). The sets of covariates were adjusted: Model 1 consisted of age, sex; Model 2 consisted of Model 1 plus region, nation, marital status, and education level; Model 3 consisted of Model 2 together with smoke now status, physical activity, excessive drinking status, oil intake, salt intake and family history of diabetes, BMI. Sensitivity analysis was performed after redefining MetS according to the criteria of ATP. Stratified analysis was carried out according to different age, sex, and BMI to explore whether specific factors change correlation. All analyses were

performed by using SPSS 25.0 and R3.6.3, and statistical significance was based on 2-side test at the 0.05 significance level.

Results

Baseline Characteristics of participants

The baseline characteristics in different groups are presented in Table 1. Participants has the highest BMI of $26.2 \pm 3.68\text{kg/m}^2$ in the MetS and depression group. Individuals are more often women, the Han nationality across the four groups. No MetS and depression and MetS only were more likely to live in rural. People in the groups of MetS only, MetS comorbidity with depression were older compared with those with no MetS and depression. Overall, 8165 individuals were tracked during 10-years follow up, 678 new cases of incident T2DM were documented.

Table 1
The baseline characteristics of the participants.

Character	Total (n = 6489)	No MetS or depression (n = 5097)	Depression only (n = 344)	MetS Only (n = 979)	MetS and depression (n = 69)	P value
T2DM(%)						< 0.001
Yes	678	464	38	159	17	
No	5811	4633	306	820	52	
Age (years)	43.4 ± 14.96	42.2 ± 14.85	44.4 ± 14.34	49.2 ± 14.45	49.1 ± 12.37	< 0.001
BMI(kg/)	22.8 ± 3.31	22.3 ± 2.89	22.00 ± 2.48	25.5 ± 4.02	26.2 ± 3.68	< 0.001
Sex (%)						0.003
Male	3080(47.5)	2437(47.8)	139(40.4)	481(49.1)	23(33.3)	
Female	3409(52.5)	2660(52.2)	205(59.6)	498(50.9)	46(66.7)	
Region n (%)						< 0.001
Urban	2368(36.5)	1904(37.4)	172(50.0)	254(25.9)	38(55.1)	
Rural	4121(63.5)	3193(62.6)	172(50.0)	725(74.1)	31(44.9)	
Nation n (%)						0.001
The Han nationality	3844(59.2)	2964(58.2)	224(65.1)	604(61.7)	52(75.4)	
Other	2645(40.8)	2133(41.8)	120(34.9)	375(38.3)	17(24.6)	
Education level n (%)						< 0.001
No formal school	2268(35.0)	1767(34.7)	162(47.1)	306(31.3)	33(47.8)	
Primary	1349(20.8)	1082(21.2)	57(16.6)	197(20.1)	13(18.8)	
Middle school	1974(30.4)	1552(30.5)	86(25.0)	318(32.5)	18(26.1)	
High school	587(9.0)	456(8.9)	21(6.1)	106(10.8)	4(5.8)	
College/university or more	311(4.8)	240(4.7)	18(5.2)	52(5.3)	1(1.4)	
Marital status, n (%)						0.728

Character	Total (n = 6489)	No MetS or depression (n = 5097)	Depression only (n = 344)	MetS Only (n = 979)	MetS and depression (n = 69)	<i>P</i> value
Married	5208(80.3)	4094(80.3)	281(81.7)	776(79.3)	57(82.6)	
Other	1281(19.7)	1003(19.7)	63(18.3)	203(20.7)	12(17.4)	
Smoke now						0.044
Everyday	1645(25.4)	1272(25.0)	76(22.1)	285(29.1)	12(17.4)	
Sometime	195(3.0)	152(3.0)	9(2.6)	32(3.3)	2(2.9)	
Never	4649(71.6)	3673(72.0)	259(75.3)	662(67.6)	55(79.7)	
Excessive drinking						0.004
No	5837(90.0)	4606(90.4)	311(90.4)	853(87.1)	67(97.1)	
Yes	652(10.0)	491(9.6)	33(9.6)	126(12.9)	2(2.9)	
Physical activity						0.005
Never	5922(91.3)	4683(91.9)	313(91.0)	864(88.3)	62(89.9)	
1–2 days per week	162(2.5)	116(2.3)	14(4.1)	30(3.1)	2(2.9)	
≥ 3 days per week	405(6.2)	298(5.8)	17(4.9)	85(8.7)	5(7.2)	
Family history of diabetes						0.006
No	6399(98.6)	5039(98.9)	334(97.1)	959(98.0)	67(97.1)	
Yes	90(1.4)	58(11.1)	10(2.9)	20(2.0)	2(2.9)	
Salt intake 6g/day						0.348
No	1916(29.5)	1515(29.7)	111(32.3)	282(28.8)	16(23.2)	
Yes	4573(70.5)	3582(70.3)	233(67.7)	697(71.2)	53(76.8)	
Oil intake 25g/day						0.023
No	1916(29.5)	1549(30.4)	97(28.2)	250(25.5)	20(29.0)	
Yes	4573(70.5)	3548(69.6)	247(71.8)	729(74.5)	49(71.0)	

Independent and synergistical effect of MetS and depression on T2DM

As shown in Table 2, the incidence rate of T2DM was 13.32 and 16.79 in the groups of depression and MetS. We explored the independent effect of depression or MetS on the occurrence of T2DM. Statistically significant results were observed between depression with no depression after adjustment for covariates 1.31(1.01–1.68). Similarly, compared to participants with no MetS, the incidence was approximately two times stronger predictor of T2DM (RR, 1.65, 95% CI, 1.40–1.94) for MetS patients. After further adjustment for region, nation, marital status, and education level, smoke now status, excessive drinking status, physical activity, oil intake, salt intake, family history of diabetes, and BMI, the risk ratio remained statistically significant (RR, 1.45, 95% CI, 1.22–1.72).

It is noteworthy that MetS combined with depression, as a multimorbidity status, was synergistically linked to argued incidence of T2DM, as showed by RR 2.49(1.64,3.79), and the risk was more higher than that of MetS only 1.61(1.36,1.91)) or depression only 1.18(0.87,1.61)). After adjustment for model1 + current smoking status, physical activity, excessive drinking status, oil intake, salt intake, family history of diabetes, and BMI, the RR is 2.11(1.39,3.22) and *P* value remains significance, as shown in Table 3.

Table 2 Independent association of MetS or depression with risk of incident type 2 diabetes.

Subgroup	Case/Total	Incidence rate (%)	Model 1	Model 2	Model 3
Depression					
No	623/6076	10.25	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	55/413	13.32	1.27(0.99-1.64)	1.31(1.01-1.68)	1.33(1.03-1.71)
MetS					
No	502/5441	9.23	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Yes	176/1048	16.79	1.65(1.40-1.94)	1.61(1.37-1.90)	1.45(1.22-1.72)

Abbreviations: RR, risk ratio; CI, confidence interval.

Model 1: adjusted for age, sex.

Model 2: model 1 plus region, nation, marital status, and education level.

Model 3: model 2 plus smoke now status, excessive drinking status, physical activity, oil intake, salt intake and family history of diabetes, BMI.

Table 3
 Combined effect of MetS and depression status and risk of incident type 2 diabetes.

MetS or depression status	Case/Total	Incidence rate (%)	Model 1	Model 2	Model 3
No MetS and depression	464/5097	9.1	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Depression only	38/344	11.0	1.18(0.87,1.61)	1.20(0.88,1.63)	1.23(0.90,1.67)
MetS only	159/979	16.2	1.61(1.36,1.91)	1.57(1.32,1.86)	1.33(1.11,1.59)
MetS and depression	17/69	24.6	2.49(1.64,3.79)	2.51(1.65,3.81)	2.11(1.39,3.22)
Abbreviations: RR, risk ratio; CI, confidence interval.					
Model 1: adjusted for age, sex.					
Model 2: model 1 plus region, nation, marital status, and education level.					
Model 3: model 2 plus smoke now status, excessive drinking status, physical activity, oil intake, salt intake and family history of diabetes, BMI.					

Subgroup Analysis and Effect Modification

The baseline population was stratified by age (< 60 years old, ≥60 years old), sex (male, female), BMI (≥ 24kg/m², < 24kg/m²) to explore the modify effect of the above major characteristics on the association between depression combined with MetS incidence of T2DM. Compared with the population who with no MetS and depression, individuals with MetS combined with depression had a significantly higher incidence of T2DM in the subgroups of age≥60 years(RR (95%CI) 3.21(1.67,6.17)), male (RR (95%CI) 2.22(1.02,4.84)), BMI ≥ 24kg/m² (RR (95%CI) 2.46(1.54,3.94)) after fully adjusting potential confounding factors. Of the association for MetS combined with depression with risk of T2DM is more obvious in those aged 60 years or older, males, and overweight population. The subgroup analysis is shown in Fig. 2.

Sensitivity analysis

The relationship between MetS combined with depression and T2DM after redefined criteria of MetS was also analyzed according to the diagnostic criteria of ATP . Compared with individuals with no MetS and depression, the RR (95%CI) value of people with MetS and depression were (1.31(0.95-1.79) and 1.84(1.22-2.78)) after adjusting Model 1 and Model 3. Table 4 depicts the sensitivity analysis.

Table 4
Sensitivity analysis using different definition of MetS.

Subgroup	Case/Total	Incidence rate (%)	Model 1	Model 2	Model 3
No MetS and depression	418/4771	8.76	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Depression only	36/318	11.32	1.26(0.92–1.73)	1.28(0.92–1.76)	1.31(0.95–1.79)
MetS only	205/1305	15.71	1.67(1.42–1.95)	1.61(1.37–1.89)	1.38(1.16–1.64)
MetS and depression	19/95	20.00	2.17(1.44–3.28)	2.15(1.42–3.23)	1.84(1.22–2.78)
Abbreviations: RR, risk ratio; CI, confidence interval.					
Model 1: adjusted for age, sex.					
Model 2: model 1 plus region, nation, marital status, and education level.					
Model 3: model 2 plus smoke now status, excessive drinking status, physical activity, oil intake, salt intake and family history of diabetes, BMI.					

Discussion

T2DM is a multi-factorial disease and various common chronic diseases or pathological status are closely related to initiation of T2DM. therefore, more attention should be paid to explore whether multimorbidity of diseases or pathological status could synergistically promote the occurrence of T2DM. To our best knowledge, this is the first prospective study to demonstrate the combined effect of MetS and depression on the susceptibility of T2DM from a position of multimorbidity. In this general population-based prospective study of Chinese adults, we uncovered that MetS and depression are independently associated with an increased risk of T2DM. More importantly, the combined exposure of MetS and depression was more strongly associated with the risk of T2DM when compared with exposure to single disease. It is noteworthy that a growing risk of T2DM with MetS combined with depression was more apparent in the population of age \geq 60 years, male, overweight.

Several cohort studies have shown that MetS was associated with an increased risk of T2DM, which was further verified among southwest China general population presented in our study. Moreover, a study showed that the MetS is associated with a 5-fold increased risk for incident T2DM[31]. The risk of DM with MetS at baseline was twice over those who with non-MetS, as evidenced by a 4-year follow-up study[32]. Based on Guizhou general population study, we determined that the presence of MetS increased 45% risk of T2DM. However, the detailed underlying mechanisms that responsible for the positive correlation between MetS and T2DM is largely unknown. But there are several potential biological mechanisms may partially explain for these founds. First, obesity and insulin resistance are

commonly co-occurrence on MetS patients [31]. Insulin resistance, one of key component of MetS, is present in many metabolic disorders, such as T2DM and MetS, and is responsible for many metabolic perturbations. Second, MetS and T2DM share many common risk factors, including age, overweight or obese, nutrition and lifestyle modification [33, 34].

Similarly, previous studies have shown that depression also increases the risk of T2DM. Luo, et al found that depressive symptoms present as a risk factor for DM among elderly[35]. Moreover, a prospective study evaluated the correlation between severe depressive episode and T2DM in China[36], which is in line with our study. Pathophysiological mechanisms by which depression increases risk of T2DM also have been explained. First of all, depression was related to hyperactivity of hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system, which contributed to the increased release of counterregulatory hormones, resulting in abdominal adiposity and insulin resistance[18, 22]. Second, dysregulated immune system functions as a mediator mechanism between depression and increased risk of T2DM. Furthermore, increased C reactive protein, TNF- α , and proinflammatory cytokines are also found to be associated with both depression and T2DM[37-39]. Collectively, the above biological mechanisms may responsible for the depression-related increased risk of T2DM.

Due to the improvement of lifestyle and increasingly social stress, the probability of people simultaneously suffering from metabolic disorder and mental illness has greatly increased. We found that MetS combined with depression could synergistically associated with increased risk of T2DM, which is more higher than that MetS only or depression only, suggesting that MetS and depression may have a superimposed effect on the occurrence of T2DM. However, the underlying mechanisms for the combined effects for T2DM need further determined. It is well-established that multiple organ damage is more likely to increase the risk of various complications than single organ damage. Other plausible reason is that both MetS and depression could induce systemic proinflammatory responses which was a key feature of T2DM [40, 41]. As the action mode of mechanistic pathways underlying the relationships of depression or MetS with risk of T2DM are similar. Therefore, the multiplicative effect of both depression and MetS might contribute to the substantially stronger pro-pathogenic effect of the multimorbidity of depression and MetS on T2DM risk. Thus, the people who suffer both depression and MetS could generate more sever inflammatory reaction, which makes people with comorbidity of MetS and depression have an apparently increased risk of T2DM. Our finding imply that individuals with MetS combined with depression should be more severely targeted for preventing and screening T2DM.

In the stratified analysis, we found that patients with depression and MetS are more likely to suffer from T2DM among the population with age > 60 years, male, overweight, and the above results was consistent with previous studies[33, 34]. Our results suggested that people with BMI \geq 24 kg/m² and abnormal metabolic should be taken seriously in Chinese for prevention and delay the occurrence of T2DM. Hence, adopting a healthy lifestyle pattern and weight loss is a major determinant to reach maximize effectiveness for decreasing the risk of T2DM.

The strengths of our study were its long duration of follow-up and its prospective cohort study design, which firstly prospective study the impact of depression combined with MetS on the incidence of T2DM. However, our study has several potential limitations. First of all, although we excluded patients with T2DM at baseline, we cannot conclude that whether the people of depression at baseline are not caused by T2DM, because a bidirectional relationship between T2DM and depression, which may cause some deviation. Second, some participants were loss to follow up as well as some missing information regarding confounders. However, sufficient number events and a high follow-up rate provided sufficient statistic power. Finally, the enrolled participants were only restricted in Guizhou Province, China. So, the extrapolation of the results should be cautious. Therefore, further prospective large-scale studies are needed to verify these results in other regional populations.

Conclusion

In conclusion, this study indicated depression and MetS are associated with increased T2DM. People who simultaneously with depression and MetS have an apparent higher risk of T2DM than those with depression or metabolic syndrome alone. Our result highlight that the multimorbidity of metabolic disorder and psychological disorder is more suffering from T2DM. Therefore, it is meaningful to prevent and effective treat metabolic disorders and mental problems, especially for MetS and depression to improve current health and reduce the risk of future T2DM. Our study provides additive value for preventing the development of T2DM from the position of prevention and control multimorbidity. Additional studies or randomized control trails are needed to confirm our conclusions and to further examine underlying mechanisms for the multimorbidity of depression and MetS with enhanced risk of T2DM.

Declarations

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Authors' contributions

K.M.T. and T.L. conceived and designed the study. K.M.T., S.Y.Z, B.Z.,Y.Y.W., X.Y.D., S.L.C. and T.L. participated in the data acquisition. K.M.T. and S.Y.Z., analyzed the data. L.L. and T.L. gave advice on methodology. K.M.T. and S.Y.Z., drafted the manuscript, and K.M.T., S.Y.Z.,B.Z., Y.Y.W., X.Y.D., S.L.C. and T.L. revised the manuscript. S.L.C. and T.L. are the guarantors of this work and had full access to all the data in the study and takes responsibility for its integrity and the accuracy of the data analysis.

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Data Availability

The aggregate data analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was conducted in accordance with the ethical standards required in the Declaration of Helsinki. This study is not related to human clinical trials or animal experiments. This study was approved by the institutional Review Committee of Guizhou Center for Disease Control and Prevention (No.S2017-02). All participants signed written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

References

1. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition[J]. *Diabetes Research and Clinical Practice*, 2019,157: 107843.
2. Zheng Y, Ley S H, Hu F B. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications[J]. *Nature Reviews Endocrinology*, 2018,14(2): 88-98.
3. Wang L, Peng W, Zhao Z, et al. Prevalence and Treatment of Diabetes in China, 2013-2018[J]. *JAMA*, 2021,326(24): 2498-2506.
4. Williams R, Karuranga S, Malanda B, et al. Global and regional estimates and projections of diabetes-related health expenditure: Results from the International Diabetes Federation Diabetes Atlas, 9th edition[J]. *Diabetes Research and Clinical Practice*, 2020,162: 108072.
5. Chatterjee S, Khunti K, Davies M J. Type 2 diabetes[J]. *Lancet*, 2017,389(10085): 2239-2251.
6. Hackett R A, Steptoe A. Type 2 diabetes mellitus and psychological stress - a modifiable risk factor[J]. *Nat Rev Endocrinol*, 2017,13(9): 547-560.
7. Athyros V G, Doumas M, Imprialos K P, et al. Diabetes and lipid metabolism[J]. *Hormones (Athens)*, 2018,17(1): 61-67.
8. Sun Y, Gao H Y, Fan Z Y, et al. Metabolomics Signatures in Type 2 Diabetes: A Systematic Review and Integrative Analysis[J]. *J Clin Endocrinol Metab*, 2020,105(4): 1000-1008.

9. Ford E S, Li C, Sattar N. Metabolic Syndrome and Incident Diabetes[J]. *Diabetes Care*, 2008,31(9): 1898-1904.
10. Lee M, Han K, Kim M K, et al. Changes in metabolic syndrome and its components and the risk of type 2 diabetes: a nationwide cohort study[J]. *Scientific Reports*, 2020,10(1).
11. Lee M, Han K, Kim M K, et al. Combinations of metabolic syndrome components and the risk of type 2 diabetes mellitus: A nationwide cohort study[J]. *Diabetes Research and Clinical Practice*, 2020,165: 108237.
12. Antonio Villa N E, Bello Chavolla O Y, Vargas Vázquez A, et al. The combination of insulin resistance and visceral adipose tissue estimation improves the performance of metabolic syndrome as a predictor of type 2 diabetes[J]. *Diabetic Medicine*, 2020,37(7): 1192-1201.
13. Tinetti M E, Fried T R, Boyd C M. Designing health care for the most common chronic condition—multimorbidity[J]. *JAMA*, 2012,307(23): 2493-2494.
14. Saklayen M G. The Global Epidemic of the Metabolic Syndrome[J]. *Current Hypertension Reports*, 2018,20(2): 12.
15. Ranasinghe P, Mathangasinghe Y, Jayawardena R, et al. Prevalence and trends of metabolic syndrome among adults in the asia-pacific region: a systematic review[J]. *BMC Public Health*, 2017,17(1): 109-118.
16. Fiest K M, Walker J R, Bernstein C N, et al. Systematic review and meta-analysis of interventions for depression and anxiety in persons with multiple sclerosis[J]. *Multiple Sclerosis and Related Disorders*, 2016,5: 12-26.
17. Wayne J K. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness[J]. *Biological Psychiatry*, 2003,54(3): 216-226.
18. Yu M, Zhang X, Lu F, et al. Depression and Risk for Diabetes: A Meta-Analysis[J]. *Canadian Journal of Diabetes*, 2015,39(4): 266-272.
19. Hoffmann M S, Brunoni A R, Stringaris A, et al. Common and specific aspects of anxiety and depression and the metabolic syndrome[J]. *J Psychiatr Res*, 2021,137: 117-125.
20. Pimenta A M, Lahortiga-Ramos F, Sayon-Orea C, et al. Depression and metabolic syndrome in participants of the "Seguimiento Universidad de Navarra" (SUN) cohort study[J]. *J Affect Disord*, 2021,284: 183-189.
21. Zhang M, Chen J, Yin Z, et al. The association between depression and metabolic syndrome and its components: a bidirectional two-sample Mendelian randomization study[J]. *Transl Psychiatry*, 2021,11(1): 633.
22. Knol M J, Twisk J W R, Beekman A T F, et al. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis[J]. *Diabetologia*, 2006,49(5): 837-845.
23. Lee Y B, Kim D H, Kim S M, et al. Risk of type 2 diabetes according to the cumulative exposure to metabolic syndrome or obesity: A nationwide population-based study[J]. *J Diabetes Investig*, 2020,11(6): 1583-1593.

24. Zhang P, Lou P, Chang G, et al. Combined effects of sleep quality and depression on quality of life in patients with type 2 diabetes[J]. *BMC Fam Pract*, 2016,17: 40.
25. Mastrototaro L, Roden M. Insulin resistance and insulin sensitizing agents[J]. *Metabolism*, 2021,125: 154892.
26. Chobanian A V, Bakris G L, Black H R, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report[J]. *JAMA*, 2003,289(19): 2560-2572.
27. He C, Levis B, Riehm K E, et al. The Accuracy of the Patient Health Questionnaire-9 Algorithm for Screening to Detect Major Depression: An Individual Participant Data Meta-Analysis[J]. *Psychotherapy and Psychosomatics*, 2020,89(1): 25-37.
28. Zimmerman M. Using the 9-Item Patient Health Questionnaire to Screen for and Monitor Depression[J]. *JAMA*, 2019,322(21): 2125-2126.
29. Kurt Kroenke R L S J. The PHQ-9: validity of a brief depression severity measure[J]. *J Gen Intern Med*, 2001,16(9): 606-613.
30. Grundy S M, Cleeman J I, Daniels S R, et al. Diagnosis and Management of the Metabolic Syndrome[J]. *Circulation*, 2005,112(17): 2735-2752.
31. Cornier M, Dabelea D, Hernandez T L, et al. The Metabolic Syndrome[J]. *Endocrine Reviews*, 2008,29(7): 777-822.
32. Udell J A, Steg P G, Scirica B M, et al. Metabolic syndrome, diabetes mellitus, or both and cardiovascular risk in outpatients with or at risk for atherothrombosis[J]. *European Journal of Preventive Cardiology*, 2013,21(12): 1531-1540.
33. Magkos F, Yannakoulia M, Chan J L. Management of the Metabolic Syndrome and Type 2 Diabetes Through Lifestyle Modification[J]. *Annu Rev Nutr*, 2009(29): 223-256.
34. Hu F B, Manson J E, Stampfer M J, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women[J]. *N Engl J Med*, 2001,11(345): 790-797.
35. Luo Y, Zhu D, Nicholas S, et al. Depressive symptoms, health behaviors and risk of diabetes in Chinese mid-aged and older adults. [J]. *Journal of Affective Disorders*, 2018,246(1): 783-788.
36. Ruiwei Meng N L C Y. Association between major depressive episode and risk of type 2 diabetes: a large study in Chinese adults[J]. *Journal of Affective Disorders*, 2018: 59-66.
37. Pradhan A D, Manson J E, Rifai N, et al. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus[J]. *JAMA*, 2001,286(3): 327-334.
38. Kiecolt-Glaser J K, Glaser R. Depression and immune function: central pathways to morbidity and mortality[J]. *J Psychosom Res*, 2002,53(4): 873-876.
39. Lainampetch J, Panprathip P, Phosat C, et al. Association of Tumor Necrosis Factor Alpha, Interleukin 6, and C-Reactive Protein with the Risk of Developing Type 2 Diabetes: A Retrospective Cohort Study of Rural Thais[J]. *Journal of Diabetes Research*, 2019,2019: 1-9.

40. Kemp K, Rose B, Herder C, et al. Inflammation in Metabolic Syndrome and Type 2 Diabetes: Impact of Dietary Glucose[J]. Annals of the New York Academy of Sciences, 2006,1084(1): 30-48.
41. Kiecolt-Glaser J K, Derry H M, Fagundes C P. Inflammation: depression fans the flames and feasts on the heat[J]. Am J Psychiatry, 2015,172(11): 1075-1091.

Figures

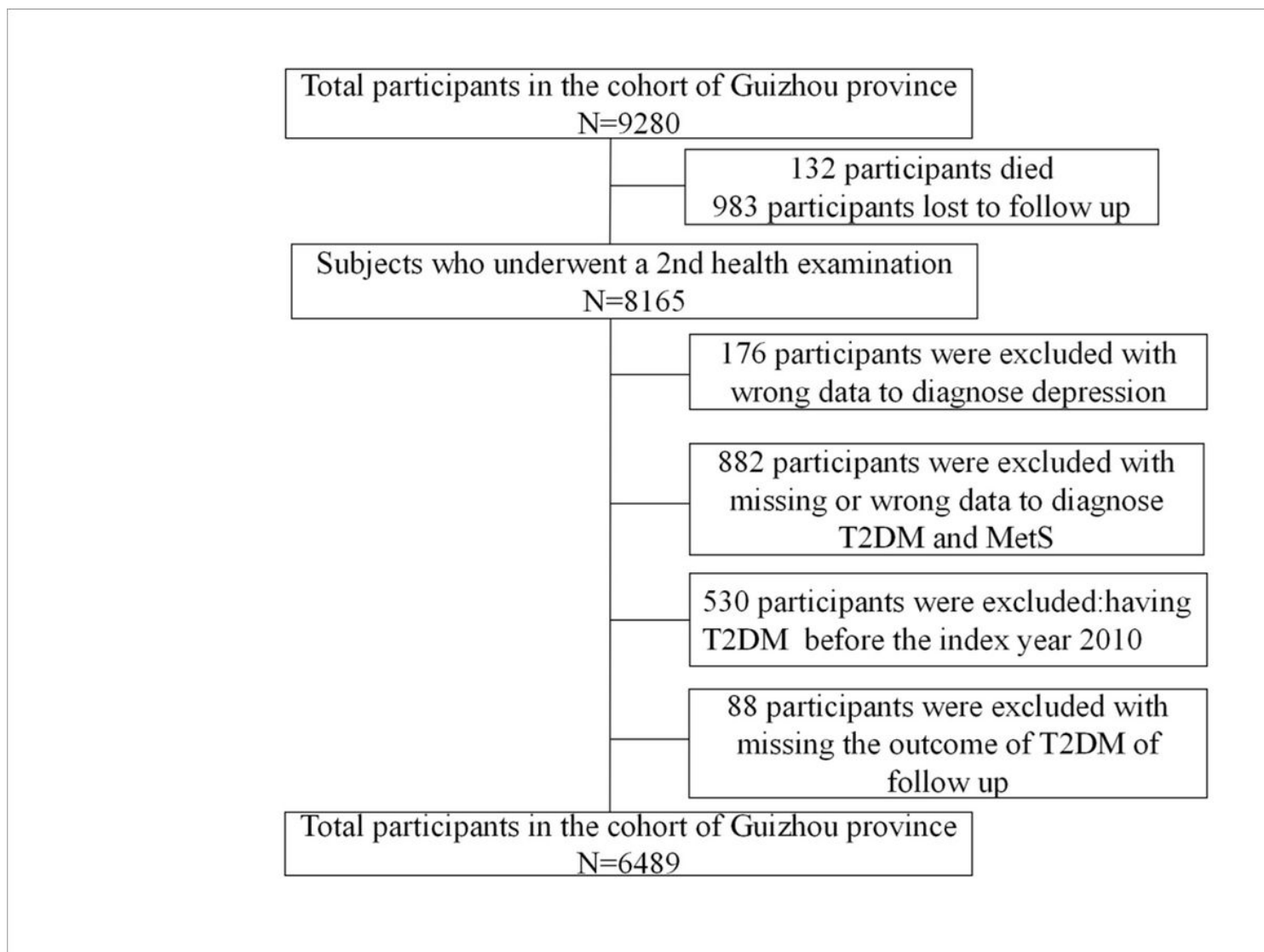


Figure 1

Flowchart of the study sample

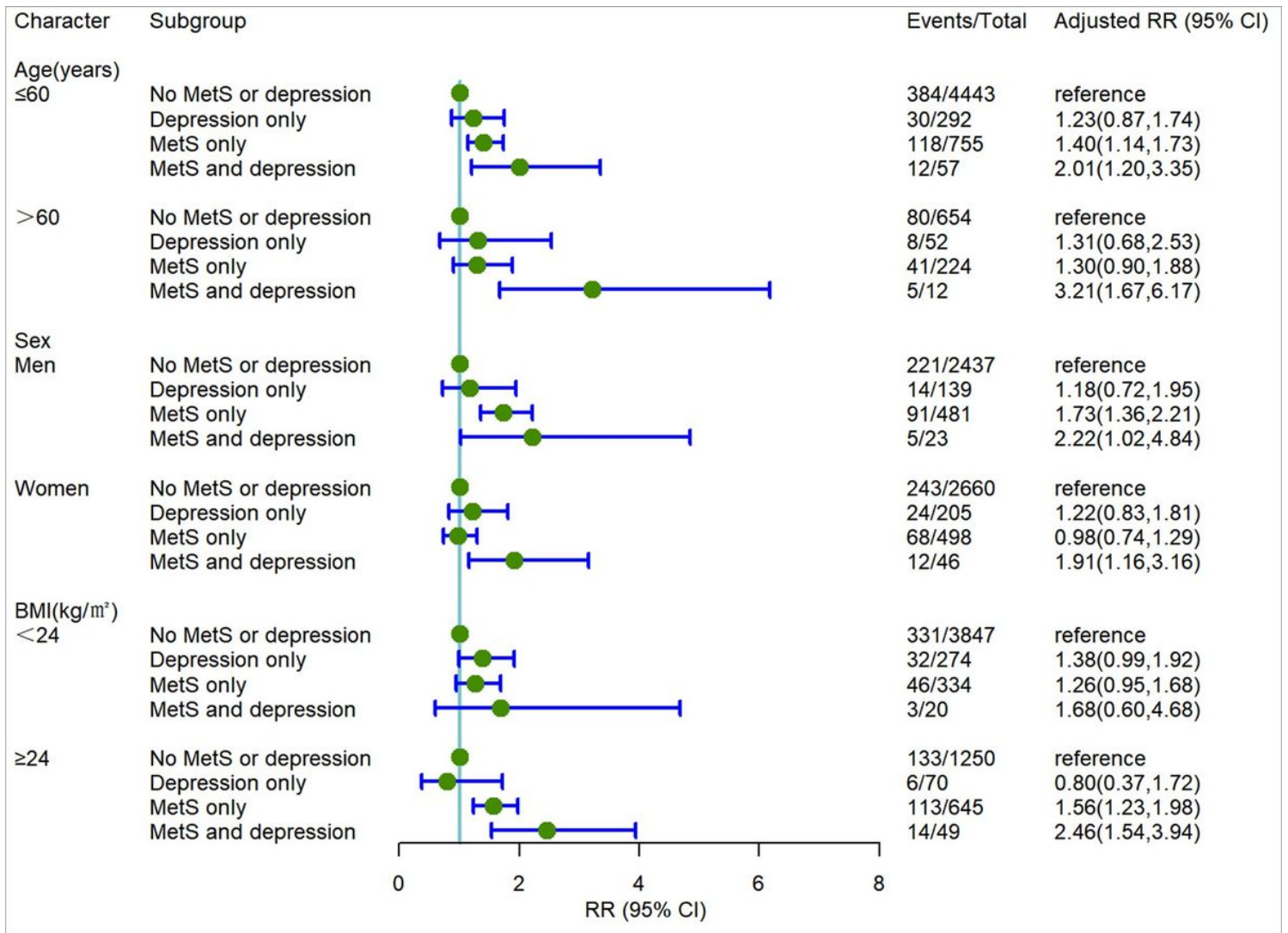


Figure 2

The incident risk of T2DM associated with MetS and depression by age, sex, BMI.

All analyses adjusted for model 3 covariates. Abbreviations: RR, risk ratio; CI, confidence interval; BMI: body mass index.