Purpose: Depression and anxiety are common disorders in patients suffering from type 2 diabetes. These disorders can lead to premature morbidity, exacerbate disease complications, make patients suffer more, and increase health-care costs. As diabetes has increased worldwide recently, it is necessary to reduce the prevalence of factors that are associated with depression and anxiety in diabetes patients. This study aimed to assess the prevalence of anxiety and depression and to identify their associated factors, including metabolic components among people with type 2 diabetes.

Patients and Methods: We performed a cross-sectional study in 1500 patients with type 2 diabetes in Kerman, in the southern part of Iran. The prevalence of depression and anxiety was estimated using the Beck Depression Inventory and the Hamilton Anxiety questionnaires, respectively. After calculating the proportions of depression and anxiety, univariate logistic regression was performed. Factors whose $P$-values were smaller than 0.2 in univariate logistic regression were included in multiple logistic regression for confounder adjustments. The analysis was performed using SPSS version 20.

Results: The rates of depression and anxiety were 59% (95% CI: 54.48–63.12) and 62% (95% CI: 59.51–66.27), respectively. Factors found to be independently associated with anxiety were high FBS, high LDL-C, high TG, hypertension, complications, low physical activity. Factors found to be independently associated with depression were female gender, older age, high BMI, high FBS, high LDL-C, low HDL-C, high TG, high HbA1c, hypertension, and low physical activity. Complications were independently associated with anxiety but not with depression. Female gender, older age, high BMI, low HDL-C, and high HbA1c were independently associated with depression but not with anxiety.

Conclusion: Current findings demonstrated that a large proportion of patients with type 2 diabetes suffer from depression and anxiety. This study also identified factors associated with these disorders. Controlling some metabolic variables will decrease the prevalence of these disorders and improves clinical remedy and quality of life in patients with type 2 diabetes.

Keywords: anxiety, depression, type 2 diabetes, Hamilton questionnaire, Beck questionnaire

Introduction
The prevalence of diabetes is increasing globally. Almost 285 million people are suffering from diabetes, and this number is expected to be increased to 438 million by 2030.¹

Diabetic patients suffer from anxiety and depression almost twice as much as the general population.² In the general population, the 12-month prevalence of anxiety and depression was 18% and 10%, respectively.³ The prevalence of anxiety and depression disorders in type 2 diabetes is approximately 60% higher than the
The complications of anxiety and depression affect all populations globally, but more than two-thirds of people who are suffering from these two disorders are living in developing countries.\textsuperscript{5} Previous studies show that anxiety and depression have an important negative impact on diabetic patients’ abilities.\textsuperscript{6} Diabetes patients that have depression and anxiety disorders usually are less physically active and show less desire to take their prescribed medications.\textsuperscript{7} Recent studies show that diabetes and depression are associated with premature mortality; these results confirm that the combination of these two diseases will significantly increase the suffering and costs of patients.\textsuperscript{8} 

The prevalence of Type 2 diabetes is about 85.5\% of all type of diabetes in Iran.\textsuperscript{9} The prevalences of depression and anxiety in Iranian patients with Type 2 diabetes are about 61.8\% and 64.5\%, respectively.\textsuperscript{10} Previous studies show that being female, having at least secondary higher cycle education, lower socioeconomic status, smoking, poorer blood sugar control,\textsuperscript{11} less physical inactivity, obesity, and excessive alcohol drinking\textsuperscript{12} are associated factors of depression and anxiety in diabetes patients. Another study demonstrated the role of hypertriglyceridemia and hypertension in increasing these disorders.\textsuperscript{13} Some studies tried to find an association between dyslipidemia other metabolic components with depression or anxiety.\textsuperscript{14} Cholesterol is an important component of the central nervous system, especially in cell membranes, and operates as the second messenger system in the brain that is related to mood stabilization.\textsuperscript{15} Anxiety is also related to an abnormal level of blood glucose, mainly among patients with severe anxiety.\textsuperscript{16} 

Management of anxiety and depression by controlling influential metabolic variables can be helpful in diminishing illness suffering, which leads to the improvement of patients, while reducing the costs of patients and health services.\textsuperscript{17} 

Despite inconsistent findings in previous studies about the association between blood metabolic variables and the severity of anxiety and depression in diabetes patients,\textsuperscript{18} there is limited information about the association among people with diabetes in developing countries, such as Iran. 

This study aimed to assess first the prevalence of anxiety and depression in a large outpatient sample of people with type 2 diabetes, and second the associated factors of anxiety and depression among patients with type 2 diabetes in southern parts of Iran.

**Materials and Methods**

**Subjects**

A total of 1500 diabetes patients 18–75 years of age were enrolled in this case-control study between August and November 2018. The presence of diabetes was defined as a fasting plasma glucose value >7.0 mmol/L (FBS>126 mg/dL).

To ensure the heterogeneity of the sample, patients were recruited from several clinical laboratories. Inclusion criteria included: Iranian nationality; a diagnosis of Type 2 diabetes at least 6 months prior to the start of the study, age 18–75 years, and not taking any medication that influences glucose tolerance (thiazide diuretics, beta-blockers, steroids, psychopharmacologic medications, particularly antipsychotics, tricyclic antidepressants, or serotonin reuptake inhibitors) apart from insulin or sulfonylureas. Exclusion criteria were: diagnosis of an underlying disease such as renal disease, history of cardiovascular disease (myocardial infarction or coronary revascularization), and cerebrovascular disease (stroke or carotid endarterectomy). Individuals with unknown or pre-diabetes status were also omitted from the study. These patients referred to laboratories in order to check their blood test. All participants were asked to complete two questionnaires. Illiterate patients completed questionnaires by face to face interview in the presence of a witness.

Full confidentiality of the data collected was ensured to all the participants and all interviews were done after the participant’s consent. The study was approved by the local ethics committee of the Kerman University of Medical Sciences (reference number: IR.KMU.REC.1397.174), and all participants provided their written informed consent prior to the beginning of the study. This study was conducted in accordance with the Declaration of Helsinki.

The following demographic, clinical, and laboratory data were recorded or determined for each patient at the moment of the inclusion in the study: age, gender, marital status, education, alcohol dependency, cigarette smoking, and complications (retinopathy, cardiomyopathies, nephropathies, and neuropathies associated with diabetes mellitus were considered as complications), depression and anxiety, weight, height, body mass index (BMI), blood pressure (BP), fasting blood sugar (FBS), glycated hemoglobin (HbA1c), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).

**Psychiatry Measurements**

The Beck Depression Inventory (BDI) questionnaire is one of the most common questionnaires that is used for
screening depression in the general population. The BDI-II, the Persian version, is used in this study, and the validity and reliability of the Persian version has been defined in the previous study. It contains 21 items, and each question has 4 options to answer, showing the severity of depressive symptoms, and a total score ranging between 0 and 63. Thereafter, 0–13 points indicate none or minimal, 14–19 points mild, 20–28 points moderate, and 29–63 points severe depressive symptoms. We considered a cut-off scale of 18 to study the population. This cut-off scale was previously used in other studies.

The Hamilton Anxiety (HA) questionnaire is a 14-item clinician-rated instrument designed to assess and quantify the severity of anxiety. Each item is rated on a five-point Likert-type scale ranging from 0 to 4. Although the scale assesses a broad range of symptoms, it is most frequently used to assess the severity of generalized anxiety disorder. HA is comprised of psychic and somatic subscales. The psychic subscale (items 1–6 and 14) evaluates the subjective cognitive and affective complaints of anxiety (anxious mood, tension, fears, difficulty concentrating); it is particularly useful in assessing the severity of generalized anxiety disorder. The somatic component (items 7–13) emphasizes features of general anxiety disorder such as autonomic arousal, as well as respiratory, gastrointestinal, and cardiovascular symptoms. Validity and reliability of the Persian version were defined in the previous study. A score of 14 considered as a threshold for clinically significant anxiety.

Laboratory Measurements
Blood samples were taken from each patient at 8:00 a.m. Serum FBS, triglyceride, cholesterol, HDL-C, and LDL-C levels were determined by BS-300MINDRAY (Shenzhen Mindray Biomedical Electronics Co., Shenzhen, China) by Roche kits (Penzberg, Germany). Arterial blood pressure (BP) was determined with a calibrated sphygmomanometer, aneroid type, and a stethoscope. Patients were seated for 10 min before the pressure was taken. BP measurements were carried out on the left and right arms and the average of two measurements was recorded as a BP value. Measurements were taken by skilled nurses.

Statistical Analysis
Descriptive statistics were computed and reported for all the variables. Bivariable and multivariable logistic regressions were performed to identify independent predictors of depression and anxiety. Variables with a P-value of less than 0.2 in the bivariable logistic regression were entered into the multivariable regression model. The variance inflation factor was assessed for multicollinearity between predictors, and no multicollinearity was detected. The final model was selected through a backward selection approach based on the likelihood ratio test and the lowest Akaike’s information criteria value. Potential interaction effects were checked at the significance level of 0.1, and none of them were significant. Crude and adjusted odds ratio (OR) with 95% confidence interval were reported. Hosmer–Lemeshow goodness of fit was run on the fully adjusted anxiety and depression models to check for an adequate fit of the data. The level of significance was set at 0.05 (two-tailed). All analyses were performed using the Statistical Package for Social Science (SPSS) version 20 for Windows.

Results
From this sample, the rates for depression and anxiety were 59% (95% CI: 54.48–63.12) and 62% (95% CI: 59.51–66.27), respectively. In this sample, the larger group was formed of females (51.3%). Most of them were married (75.3%) and mainly employed (62.0%). The socio-demographic characteristics of the participants are summarized in Table 1. The mean age was 47.12±12.52 years with range of 18–79 years old. The mean level of education was 8.91±5.13 years. Eighteen percent of patients had not received formal education or were illiterate. The mean body mass index was 27.81±5.21 with a range of 17–48. The average glucose level was 174.42±73.32 mg/dL, with a range of 70–500 mg/dL. The mean systolic BP was 121.00±13.11 (range 90–180) and the corresponding average diastolic BP was 81.13±10.72 (range 60–130). The mean HbA1c was 7.8±1.6 (range 7.1–8.2), mean LDL-C was 111.5±34.7, mean TG was 1.6±1.5 (mmol/L), and mean HDL-C was 1.5±0.4 (mmol/L). When we analyzed anxiety the average score was 17.87±11.06 (range 1–39), whereas the mean score for depression was 15.5±9.6, with a range of 1–49.

Table 2 summarizes the results of univariate and multivariate analyses of characters and metabolic variables for associations with anxiety. The variables that showed a significant positive association with increasing anxiety were high FBS level, high LDL-C, high TG, high HbA1c, hypertension, presence of complications, and lack of physical activity. In multivariable logistic regression, when univariate result was adjusted for confounding variables, high FBS level [AOR=1.38,95], high LDL-C [AOR=1.54,95], high...
Table 1 Population Characteristics According to Demographic, Metabolic and Psychopathology Status of Patients with Type 2 Diabetes

|                          | Number | Percent |
|--------------------------|--------|---------|
| Gender                   |        |         |
| Male                     | 730    | 48.7    |
| Female                   | 770    | 51.3    |
| Marital Status           |        |         |
| Married                  | 1130   | 75.3    |
| Single                   | 210    | 14.0    |
| Widowed                  | 110    | 7.3     |
| Separated/divorced       | 50     | 3.3     |
| Occupation               |        |         |
| Employed                 | 930    | 62.0    |
| Unemployed               | 570    | 38.0    |
| Age (in years)           |        |         |
| Up to 50                 | 1113   | 74.2    |
| ≥50                      | 387    | 25.8    |
| Education                |        |         |
| Up to 6 years            | 640    | 42.7    |
| >6 years of schooling    | 860    | 57.3    |
| Cigarette Smoking (Dependency) |    |         |
| Yes                      | 550    | 36.6    |
| No                       | 950    | 63.4    |
| Alcohol Abuse/Dependency |        |         |
| Yes                      | 398    | 26.6    |
| No                       | 1102   | 73.4    |
| Insulin Use              |        |         |
| Yes                      | 390    | 26.0    |
| No                       | 1110   | 74.0    |
| High BMI                 |        |         |
| Yes                      | 217    | 14.6    |
| No                       | 1283   | 85.4    |
| High FBS Level (mg/dl)   |        |         |
| Yes                      | 1281   | 85.4    |
| No                       | 219    | 14.6    |
| High LDL-C (mmol/L)      |        |         |
| Yes                      | 295    | 19.8    |
| No                       | 1205   | 80.2    |
| Low HDL-C (mmol/L)       |        |         |
| Yes                      | 195    | 12.9    |
| No                       | 1305   | 87.1    |
| High TG (mmol/L)         |        |         |
| Yes                      | 1216   | 79.0    |
| No                       | 284    | 19.0    |
| HbA1c                    |        |         |
| Yes                      | 1261   | 84.1    |
| No                       | 239    | 15.9    |
| Hypertension             |        |         |
| Yes                      | 602    | 39.1    |

(Continued)

Table 1 (Continued).

|                          | Number | Percent |
|--------------------------|--------|---------|
| Anxiety                  |        |         |
| With anxiety             | 930    | 62.0    |
| Without anxiety          | 570    | 38.0    |
| Depression               |        |         |
| With depression          | 885    | 59.0    |
| Without depression       | 615    | 41.0    |
| Complications            |        |         |
| Yes                      | 75     | 4.2     |
| No                       | 1425   | 95.8    |
| Physical Activity        |        |         |
| Yes                      | 653    | 43.5    |
| No                       | 847    | 56.5    |

Notes: High FBS: >120 (mg/dL); high BMI: ≥25 kg/m²; low HDL-C: HDL-C <1.03 (mmol/L) for men and <1.3 (mmol/L) for women; high LDL-C: LDL-C ≥4.13 (mmol/L); high TG: ≥1.7 mmol/L; high HbA1c: HbA1c >0.7 mmol/L; hypertension: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.

TG [AOR=1.2395], hypertension [AOR=1.5295], complication [AOR=1.4295] and lack of physical activities [AOR=1.3895] and were significantly associated with higher anxiety score.

Table 3 summarizes the results of univariate and multivariate analyses of characteristics and metabolic variables of associations with depression. The variables that showed a significant positive association with increasing depression were female gender, high age, BMI, high FBS level, high LDL-C, low HDL-C, high TG, high HbA1c, hypertension, and lack of physical activity. In multivariable logistic regression, when univariate result was adjusted for confounding variables, female gender [AOR=1.3895], BMI [AOR=1.3595], high FBS level [AOR=1.5195], high LDL-C [AOR=1.4295], low HDL-C [AOR=1.4895], high TG [AOR=1.3995], high HbA1c [AOR=1.5495], hypertension [AOR=1.3995], and lack of physical activities [AOR=1.6495], were significantly associated with higher depression score.

Discussion
This study estimated the prevalence of depression and anxiety in a type 2 diabetic population in Kerman located in the southern part of Iran. This study showed that low physical activity, diabetes complications, high LDL-C, high TG, high FBS level, and hypertension are
positively associated with high anxiety scores. High Age, high BMI, female gender, low physical activity, high LDL-C, low HDL-C, high TG, high FBS level, high HbA1c, and hypertension are positively associated with depression.

Several studies demonstrated that the development of co-morbid anxiety and/or depression in diabetic people leads to increased disease severity, complications, work disability, poor quality of life and increased use of medical services, and higher burden of health-care costs.8

### Table 2: Association Between Demographic and Metabolic Variables and Anxiety in Patients with Type 2 Diabetes

| Variables                               | Levels          | With Anxiety | Without Anxiety | OR (95% CI)   | P     | AOR (95% CI) | P     |
|-----------------------------------------|-----------------|--------------|-----------------|---------------|-------|--------------|-------|
| Gender N (%)                            | Male            | 388          | 342             | Ref.          | 1.12  | (0.61–1.17)  | 0.18  |
|                                         | Female          | 431          | 339             | Ref.          | 1.21  | (0.81–1.63)  | 0.15  |
| Marital Status                          | Married         | 618          | 512             | Ref.          | 0.79  | (0.57–1.23)  | 0.32  |
|                                         | Single          | 126          | 84              |               | 1.07  | (0.98–1.43)  | 0.31  |
|                                         | Widowed         | 58           | 52              |               | 1.02  | (0.89–1.18)  | 0.29  |
|                                         | Separated/divorced | 27     | 23              |               | 1.02  | (0.89–1.18)  | 0.29  |
| Occupation                              | Employed        | 430          | 500             | Ref.          | 1.19  | (0.77–1.49)  | 0.24  |
|                                         | Unemployed      | 289          | 281             | Ref.          | 1.19  | (0.77–1.49)  | 0.24  |
| Age (in years)                          | Up to 50        | 523          | 590             | Ref.          | 1.05  | (0.78–1.41)  | 0.33  |
|                                         | ≥50             | 187          | 200             |               | 1.05  | (0.78–1.41)  | 0.33  |
| Education                               | Up to 6 years   | 358          | 282             | Ref.          | 0.98  | (0.67–1.48)  | 0.26  |
|                                         | >6 years        | 473          | 387             | Ref.          | 0.98  | (0.67–1.48)  | 0.26  |
| Cigarette Smoking                       | No              | 531          | 419             | Ref.          | 0.65  | (0.31–2.11)  | 0.14  |
|                                         | Yes             | 250          | 300             |               | 0.65  | (0.31–2.11)  | 0.14  |
| Alcohol Dependency                      | No              | 465          | 637             | Ref.          | 0.66  | (0.38–1.62)  | 0.23  |
|                                         | Yes             | 130          | 268             |               | 0.66  | (0.38–1.62)  | 0.23  |
| Insulin Use Drug Treatment              | No              | 233          | 877             | Ref.          | 1.07  | (0.54–1.31)  | 0.34  |
|                                         | Yes             | 86           | 304             |               | 1.07  | (0.54–1.31)  | 0.34  |
| High BMI                                | No              | 328          | 955             | Ref.          | 0.87  | (0.48–1.38)  | 0.32  |
|                                         | Yes             | 50           | 167             |               | 0.87  | (0.48–1.38)  | 0.32  |
| High FBS Level (mg/dl)                  | No              | 112          | 107             | Ref.          | 1.42  | (0.34–1.17)  | 0.03* |
|                                         | Yes             | 767          | 514             | Ref.          | 1.42  | (0.34–1.17)  | 0.03* |
| High LDL-C (mmol/L)                     | No              | 121          | 1084            | Ref.          | 1.64  | (1.78–2.56)  | 0.02* |
|                                         | Yes             | 30           | 165             | Ref.          | 1.64  | (1.78–2.56)  | 0.02* |
| Low HDL-C (mmol/L)                      | No              | 453          | 852             | Ref.          | 1.22  | (1.03–2.08)  | 0.11  |
|                                         | Yes             | 77           | 118             | Ref.          | 1.22  | (1.03–2.08)  | 0.11  |
| High TG (mmol/L)                        | No              | 54           | 230             | Ref.          | 1.58  | (1.17–2.09)  | 0.03* |
|                                         | Yes             | 329          | 887             | Ref.          | 1.58  | (1.17–2.09)  | 0.03* |
| High HbA1c                              | No              | 43           | 196             | Ref.          | 1.44  | (1.11–1.72)  | 0.04* |
|                                         | Yes             | 302          | 959             | Ref.          | 1.44  | (1.11–1.72)  | 0.04* |
| Hypertension                            | No              | 342          | 556             | Ref.          | 2.08  | (1.64–2.31)  | 0.02* |
|                                         | Yes             | 338          | 264             | Ref.          | 2.08  | (1.64–2.31)  | 0.02* |
| Complications                           | No              | 698          | 727             | Ref.          | 1.56  | (1.08–1.79)  | 0.03* |
|                                         | Yes             | 45           | 30              | Ref.          | 1.56  | (1.08–1.79)  | 0.03* |
| Physical Activity                       | No              | 290          | 343             | Ref.          | 1.45  | (1.01–2.22)  | 0.02* |
|                                         | Yes             | 467          | 380             | Ref.          | 1.45  | (1.01–2.22)  | 0.02* |

Notes: Ref: reference category; P: P-value; high FBS: >126 (mg/dL); high BMI: ≥25 kg/m²; Low HDL-C: HDL-C <1.03 (mmol/L) for men and <1.3 (mmol/L) for woman; high LDL-C: LDL-C ≥4.13 (mmol/L); high TG: ≥1.7 mmol/L; high HbA1c: HbA1c >0.7mol/hypertension: systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. *Significant P-value.

Abbreviations: OR, odds ratio; AOR, adjusted odds ratio.
In this study, the prevalence of anxiety and depression was estimated at 59% and 62%, respectively. Two studies have analyzed its prevalence of depression in diabetic patients in Kerman, and their results were published in a systematic review study.

According to the result of this systematic review, these two research projects focused only on prevalence of depression in diabetes patients in Kerman and they did not report anxiety prevalence. The two studies exhibited a similar depression prevalence of 57% and 61%. However, their sample sizes were small (n=300 and 150).
respectively). In the present study, the sample size was increased to 1500 diabetic patients. In addition, we analyzed the frequency of anxiety in these patients. To our knowledge, this is the first study analyzing both depression and anxiety in diabetes patients in the southern part of Iran. However, we found a higher prevalence than the one reported in those studies. In fact, recent studies have shown a lower prevalence in under-developed countries.\textsuperscript{1,25}

We observed a positive association between diabetes complications and higher anxiety, but not with depression. This result is in line with the result of a previous study.\textsuperscript{26} Also, against the result of this study, a previous study showed that there is an association between neuropathy as a complication of diabetes and depression.\textsuperscript{27}

This study showed that women had higher depression score compared to men. Several previous studies confirmed a similar result, according to which females experience significantly more depression in general populations\textsuperscript{28} and among people with diabetes. A possible explanation is that women experience gender-specific events such as menarche cycles and childbirth, which expose them to handle several works and emotion at a time. This situation makes them more emotional and sensitive in comparison to men.\textsuperscript{29}

This study also showed that age is an independent factor for depression. This result is in accordance with a previous report that showed a significant association between age and depression and other psychological disorders.\textsuperscript{29} This may be due to more isolation being experienced in older age that may lead to the development of psychological conditions.\textsuperscript{30}

It is well known that physical activity is a protective barrier against depression and the development of other psychological illnesses.\textsuperscript{31} Furthermore, the negative association between physical activity and anxiety was confirmed among various groups of the population.\textsuperscript{32} This study proved that physical inactivity had an independent association with depression and anxiety.

In the current research, BMI was found to be independently associated with depression, but not anxiety. This result is in line with previous studies that identified BMI as an independent factor associated with depression among people with diabetes.\textsuperscript{33} This study showed a positive effect of high TG on depression and anxiety; this result is inconsistent with the results of a previous study that showed the effect of TG on both disorder types.\textsuperscript{1} Another study confirmed the effect of higher TG on increasing depression in type 2 diabetes patients.\textsuperscript{34} This may be due to the fact that comorbid anxiety in patients with depression may increase the levels of circulating catecholamines and increase the lipoprotein lipase activity, thus elevating the serum cholesterol and triglyceride concentrations.\textsuperscript{35}

FBS was associated with depression and anxiety, which was also confirmed in previous studies.\textsuperscript{26} HbA1c was associated with depression, but not with anxiety. This result is in line with the result of the previous study that confirms this effect on depression only.\textsuperscript{36}

Low HDL-C was also associated with increased depression and anxiety, and this result is in line with the results of a previous study conducted in the Netherlands, which confirmed the role of decreasing HLD in anxiety and depression in the general population.\textsuperscript{37} High LDL-C was associated with depression and anxiety. This result is in line with the result of a previous study in the general population in Iran\textsuperscript{38} but disagrees with studies that did not find a significant association between high LDL-C and both disorders.\textsuperscript{39} The effect of profile lipids could be explained by the fact that depression is associated with cytokine activation, which can impair cholesterol synthesis.\textsuperscript{40} There is also the possibility that cholesterol plays a causal role because it may reduce the availability of serotonin.\textsuperscript{41}

This study also confirmed the association of hypertension with both depression and anxiety. In a previous study higher diastolic blood pressure was found in female patients with diabetes compared to healthy people, but this was not significant.\textsuperscript{39}

Some limitations can be identified in this study. We did not measure depression and anxiety scores in the general population to compare with patients’ scores; our focus was to identify the predictors of depression and anxiety in diabetic patients. The depression and anxiety were measured once; to ensure more precision it is better to measure these scores several times in a period and the average scores must be identified as the final score. Therefore, we suggest that more comprehensive longitudinal studies are necessary to determine the exact effect of predictors on depression and anxiety scores in diabetic patients.

**Disclosure**

The authors report no conflicts of interest in this work.

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