Original Article

Associations between body weight change and incidence of major depressive disorder in patients with type 2 diabetes mellitus: a nationwide longitudinal follow-up cohort study of 1.1 million

Eun Young Kim[1,2,3,*], You-Bin Lee[4], Gyu-Na Lee[5], Kyungdo Han[5]
and Su-Min Jeong[1,6,7,*] [ID]

[1]Department of Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea; [2]Department of Human Systems Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Mental Health Center, Seoul National University Health Care Center, Seoul, Republic of Korea; [4]Division of Endocrinology and Metabolism, Department of Internal Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [5]Department of Statistics and Actuarial Science, Soongsil University, Seoul, Republic of Korea; [6]Department of Family Medicine, Seoul National University Health Service Center, Seoul, Republic of Korea and [7]Department of Family Medicine, Seoul National University Hospital, Seoul, Republic of Korea

Abstract

Background. Comorbid depression substantially affects the management of glycemia and diabetes-related complications among patients with type 2 diabetes mellitus. In this study, we sought to determine the association between weight change over 4 years and depression risk among patients with type 2 diabetes mellitus.

Methods. This population-based retrospective cohort study from the National Health Insurance Services of Korea included 1 111 345 patients with type 2 diabetes who were divided into groups according to body weight change over 4 years. Body weight changes were compared with the preceding 4-year period (2005–2008). Depression was defined according to the International Classification of Diseases 10th revision code for depression (F32 and F33) on one or more inpatient or outpatient claims.

Results. During a median follow-up of 7.4 years, 244 081 cases of depression were identified. We observed a U-shaped association between body weight change and depression risk with a higher risk among both groups of weight loss (hazard ratio (HR) 1.17, 95% CI 1.15–1.19 for ⩾ −10%; HR 1.07, 95% CI 1.06–1.08 for −10 to −5%) and weight gain (HR 1.06, 95% CI 1.04–1.08 for ⩾10%; HR 1.02, 95% CI 1.01–1.04 for 5–10%) compared with the stable weight group (−5 to 5%).

Conclusions. A U-shaped association between body weight change and depression risk was observed in this large nationwide cohort study. Our study suggests that patients with type 2 diabetes and weight change, either gain or loss, could be considered a high-risk group for depression.

Background

Type 2 diabetes mellitus (DM) is a chronic disease that causes life-threatening complications and substantially contributes to disability and mortality worldwide (Zheng, Ley, & Hu, 2018). The prevalence of type 2 DM has been increasing, affecting 5.9% of the global population in 2021, and is projected to increase to 9.5% (1.27 billion people) by 2050 (Ong et al., 2023). Among the key comorbidities of type 2 DM, depression primarily contributes to its mortality and disease burden of type 2 DM. It is a serious, chronic, and relapsing psychiatric disorder that is projected to be among the five leading causes of the disease burden by 2030, similar to diabetes (Mathers & Loncar, 2006). Depression is highly prevalent, affecting 16.5% of patients with type 2 DM, which is more than twice the rate of patients without DM (Anderson, Freedland, Clouse, & Lustman, 2001). Patients who were unaware of their diabetic condition had a significantly higher odds ratio (1.8, $p < 0.001$) for depression than those without DM (Meurs et al., 2016). Depression among patients with type 2 DM may have negative health outcomes such as poor glycemic control (Lustman et al., 2000), poor adherence to medical treatment (Gonzalez et al., 2007), weight gain, type 2 diabetes-related complications (Black, Markides, & Ray, 2003), and low quality of life (Bayani, Shakiba, Bijani, & Moudi, 2022). Thus, the increasing prevalence of this comorbidity has substantially increased the morbidity and mortality among patients with type 2 DM worldwide. To optimize type 2 DM

management, assessment and intervention for individuals at a high risk of comorbid depression is essential.

Among the first-line strategies for type 2 DM treatment, weight management has important clinical implications in both diabetes and comorbid depression. Current guidelines strongly recommend weight reduction among obese and overweight patients to improve glycemic control and reduce the need for hypoglycemic medications (Committee, 2021). Weight is also closely related to the risk of depression; underweight and obesity are risk factors for depression (Jung et al., 2017), and a bidirectional relationship exists between body weight and depression (Pan et al., 2012). Understanding the relationship between weight change and depression risk in individuals with type 2 DM is crucial for glycemic control and depression management.

Previous studies have mainly focused on the association between baseline body weight and depression risk; however, few studies have examined the association between weight change and depression risk (Choi et al., 2023; Zhang et al., 2022). A Korean study reported that weight variability was related to depression risk among patients with type 2 DM, suggesting that the inflammatory response resulting from weight changes and fat accumulation could contribute to the development of depression (An et al., 2021). A recent Korean study reported a U-shaped association between weight change and risk of depression among patients with diabetic kidney disease, with a more substantial association with advanced chronic kidney disease (Choi et al., 2023). A Chinese longitudinal study on 3118 middle-aged individuals demonstrated that weight loss (> −3%) over 2–4 years was associated with a 1.3 times higher depression risk of depression than stable weight (−3 to 3%) (Zhang et al., 2022). However, these previous studies had limitations, such as a specific study population prone to fluid retention and edema leading to fluctuating body weight (Choi et al., 2023), small sample size (Zhang et al., 2022), and unclear direction of body weight change (gain or loss) describing body weight variability (An et al., 2021).

Thus, we aimed to investigate the association between body weight change and depression incidence among patients with type 2 diabetes, in whom both body weight change and depression are important prognostic factors for controlling glycemia- and diabetes-related complications.

Methods

Data source and study population

We used the Korean National Health Insurance Service (NHIS) nationwide database. The Korean NHIS provides universal health insurance coverage for 97% of the Korean population, excluding 3% of Koreans in the lowest-income bracket who receive medical aid. The Korean NHIS recommends free biennial health check-ups for eligible Korean adults to assess their general health status, including a self-questionnaire on lifestyle behaviors (smoking and alcohol consumption), anthropometric measurements, and laboratory test results. Demographic and claims information for medical utilization, such as diagnosis statements coded by the International Classification of Disease 10th revision (ICD-10) and prescription statements collected by the NHIS, were provided (Cheol Seong et al., 2017). This database has been widely used in studies on various health outcomes.

We initially identified 2 746 079 patients with type 2 diabetes who underwent national health check-ups between January 2009 and December 2012. Type 2 diabetes was defined as a claim of prescribed antidiabetic medication under the diagnostic codes of type 2 diabetes (ICD-10: E11-E14) at one or more outpatient care visits or fasting plasma glucose ⩾126 mg/dL during health check-ups, called newly diagnosed type 2 diabetes. The date of the health examination between 2009 and 2012 was considered the baseline. We excluded patients aged <20 years ($n =$ 390), those without another health check-up 4 years before baseline ($n = 1 306 520$), those with a history of major depressive disorder with ICD-10 diagnostic codes (F32-F33) ($n = 248 473$), and those with missing information ($n = 79 351$), leaving a final study population of 1 111 345 individuals (×Fig. 1).

This study was approved by the Institutional Review Board of Soongsil University (IRB File No. SSU-202003-HR-201-01). The review board waived the requirement for written informed consent because publicly available and anonymous data were retrospectively analyzed.

Definition of body weight change

Body weight change was assessed using body weight measured at the first (4 years before baseline) and second (baseline) health check-ups (online Supplementary Figure 1). As national health check-ups are provided biennially in Korea, applying a 4-year interval enabled us to obtain a sufficient study population to further categorize the group by weight change and to see the effect of relatively long-term weight change. In addition, several previous studies that defined weight change over 4 years have confirmed association with various clinical outcomes.(Kim et al., 2022; Son et al., 2020) The participants were categorized into five groups according to the direction of weight change (weight gain v. weight loss) and percent change in body weight as follows: weight loss of 10% or more (⩾ −10%), weight loss of −10% to ⩾ −5%, stable weight without significant change (⩾ −5% to 5%), weight gain of 5% to 10%, and weight gain of 10% or more (⩾ 10%). This categorization was determined by analyzing the restricted cubic spline curve, depicting the relationship between body weight change as a continuous variable and incidence of depression, which exhibited a U-shaped pattern (online Supplementary Figure 2).

Study outcomes and follow-up

The primary endpoint of this study was the incidence of major depressive disorder, which we defined as a patient being diagnosed with relevant ICD-10 codes (F32: single episode and F33: recurrent) (Jin et al., 2021). The cohort was followed from the date of the second health check-up until the date of incident major depressive disorder diagnosis, death, or until the end of the study period (December 31, 2018), whichever occurred first.

Definition of covariates

Data on smoking status, alcohol consumption, and physical activity were collected using a self-administered questionnaire during the second health check-up (2009–2012). Smoking status was classified as never, former, or current smokers, and alcohol consumption was classified as none (0 g/day), mild to moderate (<30 g/day), or heavy (⩾30 g/day) based on average daily alcohol consumption (Jeong et al., 2022). Regular physical activity was defined as moderate-intensity physical activity for >30 min at least five times per week or vigorous-intensity physical activity for >20 min at least three times per week.
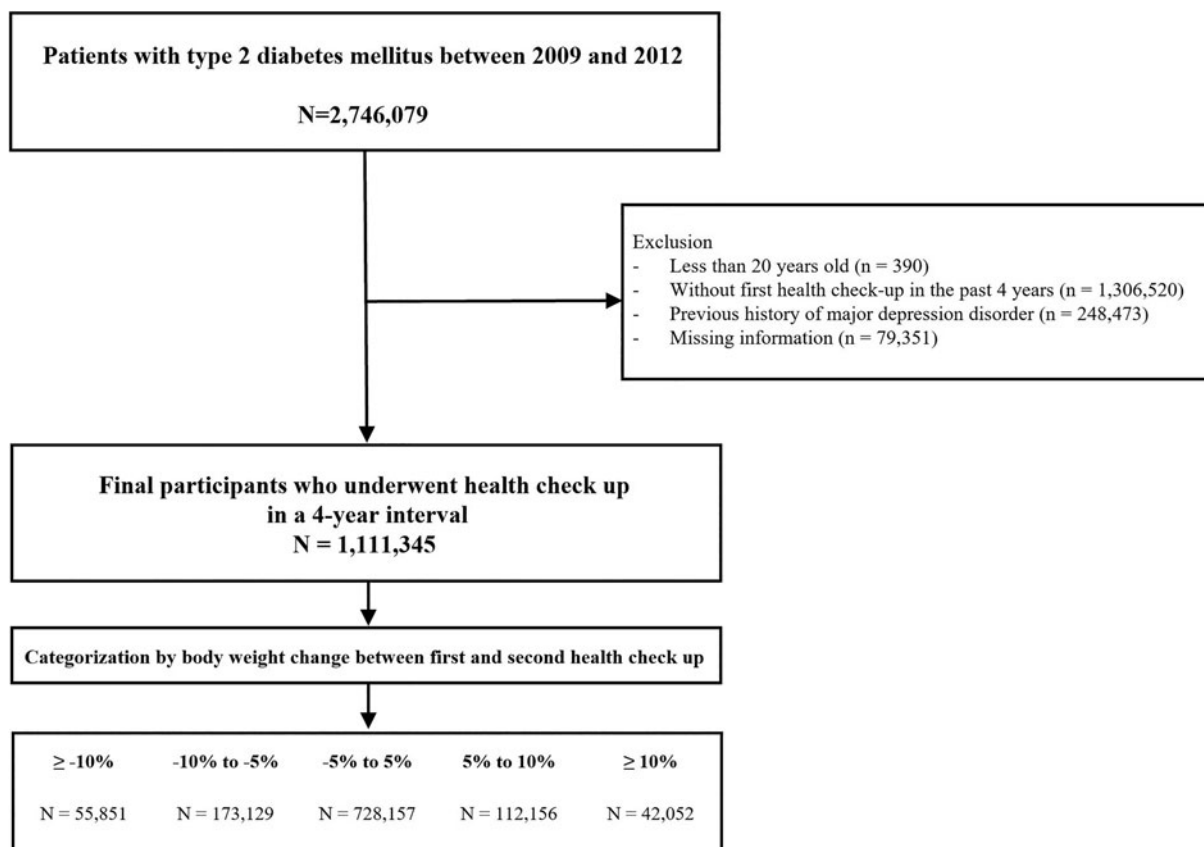
Figure 1. Flow chart of the study population.

Type 2 diabetes status was assessed based on the duration of type 2 diabetes (⩾5 years), the number of antidiabetic medications (⩾3), and insulin use. Hypertension was defined when participants had a claim with ICD-10 codes (I10-I13 or I15) and antihypertensive medication or systolic blood pressure ⩾140 mmHg or diastolic blood pressure ⩾90 mmHg at health check-ups. Dyslipidemia was defined as a claim with code E78 and lipid-lowering medications or a total cholesterol level ⩾240 mg/dL at the health check-up (Kim et al., 2018). Income level was categorized based on the monthly insurance premium as it reflects an individual's income and property.

Statistical analyses

Baseline characteristics according to groups categorized by body weight change are presented as mean ± standard deviation for continuous variables and numbers with percentages for categorical variables. Differences in body weight across the groups were compared using analysis of variance and χ^2 tests. Standardized differences were calculated to see the effect size of differences in all variables between included and excluded population (Austin, 2009). Hazard ratios (HRs) and 95% confidence intervals (CI) for the association between body weight change and depression were analyzed using Cox proportional hazards models. Participants with −5 to 5% body weight changes were regarded as the reference group. Multivariate-adjusted proportional hazards models were used. Model 1 included age and sex as the covariates. Model 2 additionally included income, smoking status, alcohol consumption, regular physical activity, and comorbidities

(hypertension, dyslipidemia, and chronic kidney disease). Model 3 included type 2 diabetes status, such as the duration of type 2 diabetes, insulin use, and number of antidiabetic medications. In the sensitivity analysis, (1) we treated body weight change as a continuous variable in both kg and %, (2) we analyzed categorical shifts based on BMI, and (3) we analyzed changes with time-lag (1-,3-and 5-year). In addition, we performed a stratified analysis by age group (<65 years v. ⩾65 years), sex, baseline BMI category, income, incidence of diabetes macrovascular and microvascular complications, diabetes duration, and presence of other psychiatric disorders to observe the different associations of these factors. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and a p-value <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

The characteristics of the study participants according to the changes in body weight are shown in ×**Table 1**. The number of participants allocated to each weight change group was 55 851 (5.0%), 173 129 (15.6%), 728 157 (65.5%), 112 156 (10.1%), and 42 052 (3.8%), respectively (weight loss: ⩾ −10%, −10% to −5%, reference: −5% to 5%, weight gain: 5% to 10%, and ⩾10%). years in the group with weight loss were more likely, older (60.7 years in the group with weight loss ⩾ −10% v. 53.3 years in the group with weight gain ⩾ 10%), and women (45.3% in the group with weight loss ⩾ −10% v. 34.9% in the

Table 1. Baseline characteristics

	Body weight change					
	⩾ −10%	−10% to −5%	−5% to 5%	5% to 10%	⩾10%	p-value
	N = 55 851	N = 173 129	N = 728 157	N = 112 156	N = 42 052	
Age, years	60.7 ± 13.1	59.3 ± 11.7	57.6 ± 11.4	55.1 ± 12.6	53.3 ± 14.3	<0.001
<40	4084 (7.3)	9410 (5.4)	47 558 (6.5)	14 693 (13.1)	8860 (21.1)	
40–64	28 133 (50.4)	103 179 (59.6)	470 007 (64.6)	69 982 (62.4)	22 971 (54.6)	
⩾65	23 634 (42.3)	60 540 (35.0)	210 592 (28.9)	27 481 (24.5)	10 221 (24.3)	
Sex						<0.001
Male	30 565 (54.7)	105 462 (60.9)	495 968 (68.1)	76 655 (68.4)	27 358 (65.1)	
Female	25 286 (45.3)	67 667 (39.1)	232 189 (31.9)	35 501 (31.7)	14 694 (34.9)	
Income, lowest Q1	11 077 (19.8)	32 219 (18.6)	125 452 (17.2)	19 568 (17.5)	7630 (18.1)	<0.001
Smoking						<0.001
Non-	33 658 (60.3)	97 545 (56.3)	377 281 (51.8)	55 768 (49.7)	21 496 (51.1)	
Former	8568 (15.3)	30 614 (17.7)	163 631 (22.5)	27 005 (24.1)	9650 (23.0)	
Current	13 625 (24.4)	44 970 (26.0)	187 245 (25.7)	29 383 (26.2)	10 906 (25.9)	
Drinking						<0.001
None	37 423 (67.0)	103 049 (59.5)	376 670 (51.7)	55 620 (49.6)	21 944 (52.2)	
Mild	14 281 (25.6)	54 920 (31.7)	276 193 (37.9)	44 212 (39.4)	15 753 (37.5)	
Heavy	4147 (7.4)	15 160 (8.8)	75 294 (10.3)	12 324 (11.0)	4355 (10.4)	
Regular exercise	11 519 (20.6)	40 280 (23.3)	169 956 (23.3)	22 835 (20.4)	7638 (18.2)	<0.001
Comorbidities						
Hypertension	31 017 (55.5)	96 286 (55.6)	410 793 (56.4)	61 558 (54.9)	22 688 (54.0)	<0.001
Dyslipidemia	21 828 (39.1)	70 372 (40.7)	296 709 (40.8)	45 739 (40.8)	16 838 (40.0)	<0.001
Chronic kidney disease	7384 (13.2)	18 732 (10.8)	74 233 (10.2)	11 756 (10.5)	4762 (11.3)	<0.001
T2DM status						
DM, duration ⩾5 years	21 190 (37.9)	66 144 (38.2)	227 483 (31.2)	27 437 (24.5)	10 256 (24.4)	<0.001
Use of insulin	7487 (13.4)	14 701 (8.5)	48 043 (6.6)	8928 (8.0)	4447(10.6)	<0.001
Number of antidiabetic medications, ⩾3	10 450 (18.7)	29 542 (17.1)	100 461 (13.8)	13 198 (11.8)	5048 (12.0)	<0.001
BMI, kg/m^2	22.6 ± 3.2	24.0 ± 3.0	25.2 ± 3.1	26.0 ± 3.5	26.8 ± 4.0	<0.001
Waist circumference, cm	81.1 ± 8.6	83.4 ± 8.0	85.9 ± 8.1	87.3 ± 8.7	88.3 ± 9.5	<0.001
Systolic BP, mmHg	126.5 ± 16.2	127.6 ± 15.5	129.0 ± 15.1	129.8 ± 15.3	130.2 ± 15.7	<0.001
Diastolic BP, mmHg	77.3 ± 10.4	78.1 ± 10.0	79.2 ± 9.9	79.9 ± 10.1	80.0 ± 10.3	<0.001
Fasting glucose, mg/dL	154.1 ± 69.3	146.9 ± 52.9	141.6 ± 39.7	140.3 ± 36.5	141.7 ± 41.1	<0.001

Total cholesterol, mg/dL	189.6 ± 45.0	192.1 ± 42.1	195.7 ± 41.1	198.8 ± 41.6	199.9 ± 42.6	<0.001
HDL -C, mg/dL	53.3 ± 23.5	52.3 ± 23.4	51.4 ± 21.9	51.5 ± 22.9	51.4 ± 22.0	<0.001
LDL -C, mg/dL	107.8 ± 41.3	109.3 ± 40.2	110.7 ± 39.8	112.0 ± 40.9	112.9 ± 42.1	<0.001
Triglyceride, mg/dLa	122.6 (122.0–123.2)	133.7 (133.4–134.1)	147.3 (147.1–147.5)	155.9 (155.4–156.4)	156.6 (155.8–157.5)	<0.001

Q1, quartile 1; CKD, Chronic kidney disease; T2DM, type 2 diabetes mellitus; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

aGeometric mean with 95% confidence interval.

Values are presented as the mean ± standard deviation for continuous variables and as numbers (%) for categorical variables.

group with weight gain ⩾10%) than in those with weight gain. smokers and non-alcohol drinkers were more prevalent among participants with weight loss than among those with weight gain. Participants with weight loss, especially with ⩾ −10%, were more likely to have ⩾5 years (37.9%) duration of type 2 diabetes, use insulin (13.4%), and be treated with three or more anti-diabetic medications (18.7%) than other groups. BMI and waist circumference increased as the degree of body weight change advanced toward weight gain. The individuals who were included were more likely to be men (66.2% *v.* 56.3%) and those with a high income (38.2% *v.* 31.4%). Despite statistically significant differences in variables between the included and excluded population, standardized differences were small except for the sex variable (0.204) (online Supplementary Table 1).

Associations between body weight change and depression incidence

During a median follow-up of 7.4 years (interquartile range 6.1–8.6), 244 081 cases of incident depression were identified (Table 2 and Fig. 2). Both weight loss (HR 1.17, 95% CI 1.15–1.19 for ⩾ −10%; HR 1.07, 95% CI 1.06–1.08 for −10% to −5%) and weight gain (HR 1.06, 95% CI 1.04–1.08 for ⩾ 10%; HR 1.02, 95% CI 1.01–1.04 for 5% to 10%) were associated with higher depression risk than the stable weight group (−5% to 5%).

In sensitivity analyses treating body weight change as a continuous variable, weight gain body weight change was associated with a lower risk of depression (HR 0.97, 95% CI 0.97–0.98 per 1SD of change in kg; and HR 0.98, 95% CI 0.97–0.98 per 1SD of change in %) (online Supplementary Table 2). Absolute change in body weight change, which reflects weight loss and weight gain, was associated with a higher risk of depression (HR 1.04, 95% CI 1.03–1.04 per 1SD of absolute change in weight (kg) and HR 1.04, 95% CI 1.03–1.04 per 1SD of absolute change in weight (%)). Categorical shifts toward weight loss from BMI 18.5–25 to BMI <18.5 and from BMI ⩾ 25 to BMI < 18.5 were associated with a higher risk of depression (HR 1.21, 95% CI 1.16–1.26 and HR 1.37, 95% CI 1.09–1.74) compared to those remaining in the same BMI category (online Supplementary Table 3). Categorical shifts toward weight gain were not significantly associated with depression risk. The lag time results were consistent with the main findings (online Supplementary Table 4).

Stratification analyses by covariates

Age- and sex-stratified analyses yielded results that were consistent with those of the total study population, revealing a U-shaped association (online Supplementary Table 5). A significant interaction between age, sex, and weight change in the incidence of depression was observed (all *p* < 0.001). A higher risk of depression related to weight loss was more prominent among participants aged <65 years than those aged ⩾65 years (HR 1.23, 95% CI 1.20–1.26 *v.* HR 1.12, 95% CI 1.10–1.15 for ⩾ −10% of weight loss). A higher risk of depression related to weight change (weight gain and weight loss) was more prominent among men than women (HR 1.29, 95% CI 1.26–1.32 *v.* HR 1.08, 95% CI 1.06–1.10 for ⩾ −10% of weight loss; HR 1.09, 95% CI 1.05–1.12 *v.* HR 1.03, 95% CI 0.99–1.06 for ⩾10% of weight gain).

A U-shaped association between body weight change and depression incidence was consistently observed across groups according to the duration of type 2 diabetes. A significant interaction was observed between body weight change and type 2

Table 2. Hazard ratios (95% confidence interval) for depression incidence according to weight change

Weight change	N	Event	Duration	IR, per 1000 PY	HR (95% CI)			
					Crude	Model 1	Model 2	Model 3
⩾ −10%	55 851	15 161	345 686.5	43.9	1.43 (1.40–1.45)	1.20 (1.18–1.22)	1.19 (1.17–1.21)	1.17 (1.15–1.19)
−10% to −5%	173 129	42 162	1 156 459.6	36.5	1.19 (1.17–1.20)	1.08 (1.07–1.09)	1.08 (1.07–1.09)	1.07 (1.06–1.08)
−5% to 5%	728 157	155 459	5 051 958.0	30.8	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
5% to 10%	112 156	22 769	778 316.7	29.3	0.95 (0.94–0.96)	1.03 (1.02–1.05)	1.03 (1.01–1.04)	1.02 (1.01–1.04)
⩾ 10%	42 052	8530	287 356.2	29.7	0.97 (0.94–0.99)	1.09 (1.06–1.11)	1.08 (1.06–1.10)	1.06 (1.04–1.08)

IR, incidence rate; PY, person-years; HR, hazard ratio; CI, confidence interval.
Model 1 was adjusted for age and sex.
Model 2 was adjusted for income, smoking status, alcohol consumption, regular physical activity, and comorbidities (hypertension, dyslipidemia, and chronic kidney disease) in addition to the covariates in Model 1.
Model 3 was adjusted for the duration of type 2 diabetes mellitus, insulin use, number of antidiabetic medications (⩾3), and covariates in model 2.

diabetes duration with respect to the incidence of depression ($p < 0.001$). Patients with newly diagnosed type 2 diabetes had a more prominent association between body weight loss (HR 1.21, 95% CI 1.16–1.26) and body weight gain (HR 1.10, 95% CI 1.05–1.14) and depression incidence than those with a type 2 diabetes duration of 1–4 years. Those who did not have other comorbid psychiatric diagnoses had a more prominent association between weight loss and the incidence of depressive disorder (HR 1.16, 95% CI 1.14–1.19) than those who had other comorbid psychiatric diagnoses (HR 1.07, 95% CI 1.04–1.09). No significant interaction was observed between body weight and depression risk based on income, baseline BMI, or incidence of macro/microvascular complications, revealing a consistent U-shaped association (online Supplementary Tables 5 and 6).

Discussion

In this large nationwide study, we investigated the relationship between body weight change and depression risk in patients with type 2 diabetes. We discovered U-shaped associations

Incidence of depression
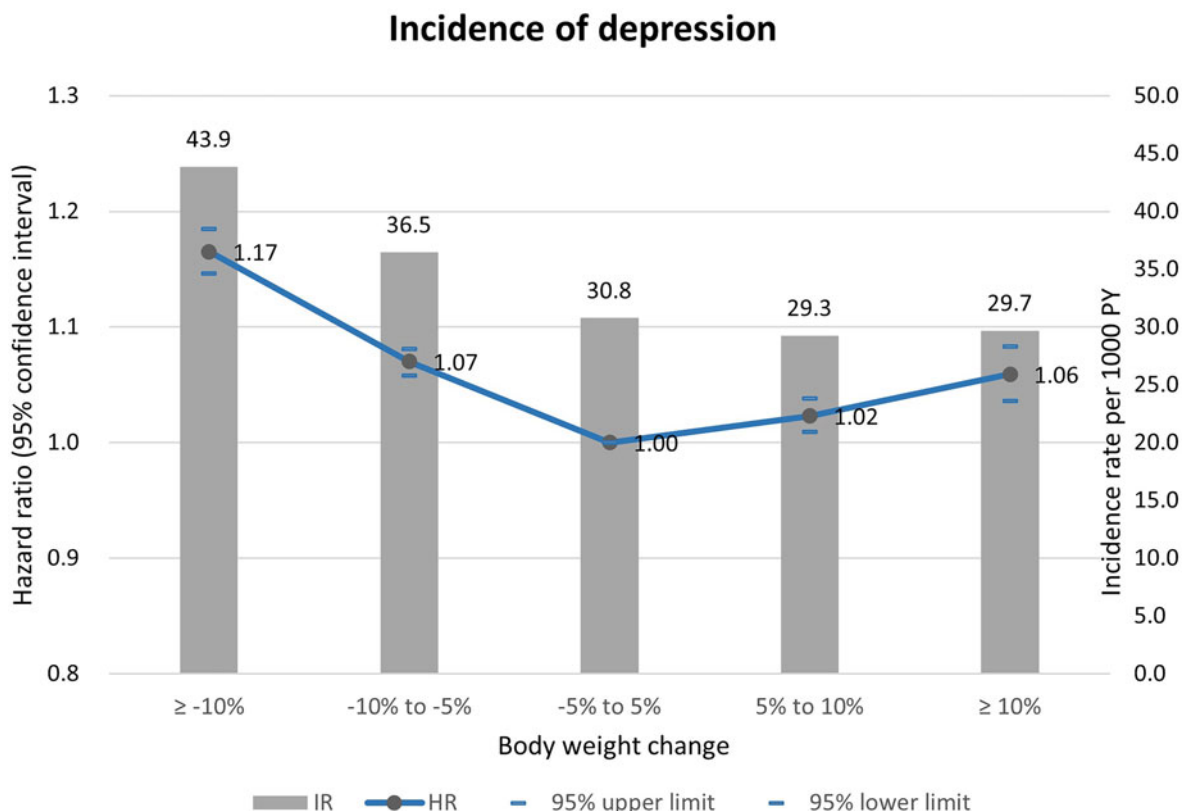
Figure 2. Associations between body weight change and risk of depression among patients with type 2 diabetes mellitus.

between body weight change and depression risk, with a 17% and 5% higher risk of depression among patients with weight loss and weight gain, respectively, than among those with stable weight. In the stratification analyses, the U-shaped association with body weight change was stronger in men, those younger than 65 years, and those with newly diagnosed type 2 diabetes than in their counterparts.

Several studies have reported that being underweight or obese was associated with depression (de Wit, van Straten, van Herten, Penninx, & Cuijpers, 2009; Jung et al., 2017), and the association between changes in body weight and depression incidence has rarely been investigated. According to a study on postmenopausal women, weight gain around menarche was associated with recurrent depression (odds ratio = 1.26, 95% CI 1.03–1.56) via insulin resistance (Perquier, Lasfargues, Mesrine, Clavel-Chapelon, & Fagherazzi, 2014). The Australian Longitudinal Study on Women's Health demonstrated that weight gain was not associated with the incidence of depression based on findings from the time-lagged analysis, suggesting possible reverse causality (Singh, Jackson, Dobson, & Mishra, 2014). However, our findings with a time lag support the hypothesis that weight change preceding depression occurrence could be a risk factor for depression in patients with type 2 diabetes. This discrepancy might be caused by the different characteristics of the study populations (healthy community people v. patients with type 2 diabetes in our study). Metabolically unhealthy individuals with obesity, rather than metabolically healthy individuals with obesity, are more likely to have an elevated risk of developing depressive symptoms, probably because of peripheral inflammatory responses to inflammatory cytokines in the brain (Hamer, Batty, & Kivimaki, 2012).

The pathophysiological mechanisms underlying the association between body weight change and depression are uncertain. Immunometabolic dysregulation, including chronic low-grade inflammation, oxidative stress, and disruption of neuroendocrine regulation (such as insulin resistance) or energy metabolism, has been proposed as a core mechanism in depression and cardiometabolic diseases (Penninx, Milaneschi, Lamers, & Vogelzangs, 2013).

First, chronic inflammation might play a key role in the association between weight change and depression. The cytokine-induced depression observed in patients with cancer or hepatitis C treated with interferon (IFN)-alpha supports the role of inflammatory processes in depression pathophysiology. IFN is frequently associated with the development of major depression in approximately 50% of patients unless prophylactically treated with antidepressants (Raison et al., 2007). In the immunometabolic depression conceptual model, a chronic low-grade inflammation cloud activates a repertoire of several behavioral symptoms (appetite and sleep alterations, fatigue, and weakness) called sickness behavior, and develops into depressive syndrome at a later stage (Milaneschi, Lamers, Berk, & Penninx, 2020). In addition, subclinical inflammation can precede weight loss and gain in older adults (Barzilay, Forsberg, Heckbert, Cushman, & Newman, 2006). Elevated concentrations of fibrinogen and C-reactive protein have also been reported before weight gain in diverse, healthy adults, and predate diminished appetite and weight loss, especially in chronic conditions (Barinas-Mitchell, Cushman, Meilahn, Tracy, & Kuller, 2001).

Second, hypothalamic-pituitary-adrenal (HPA) axis activation may be linked to weight change and depression. Urine cortisol levels were elevated in both men and women with obesity in a clinical study, revealing a U-shaped pattern between BMI and cortisol levels, with the lowest cortisol levels in overweight to class I obese groups (Schorr, Lawson, Dichtel, Klibanski, & Miller, 2015). Hypercortisolemia with caloric excess and restriction may contribute to increased adiposity and decreased bone and muscle mass, leading to weight gain and loss. Hyperactivity of the HPA axis and elevated cortisol levels in response to psychosocial stress are hallmarks of depression (Malhi & Mann, 2018). Furthermore, patients with type 2 diabetes are predisposed to high corticosteroid sensitivity and blunt responsivity to stress (for example, unchanged corticosteroid sensitivity following exposure to stress) in contrast to decreased corticosteroid sensitivity in healthy controls (Carvalho et al., 2015). Such alterations in the cortisol response among patients with type 2 diabetes may deteriorate glycemic control via insulin resistance and an enhanced cortisol effect.

Third, weight loss and gain are accompanied by unfavorable changes in body composition, such as body fat and lean body mass. During a negative energy balance, the loss of lean body mass is induced by the inhibition of protein synthesis and promotion of protein breakdown, which increases the risk of sarcopenia, especially in vulnerable populations (for example, people with type 2 diabetes) (Cava, Yeat, & Mittendorfer, 2017). During weight gain, individuals gain more fat mass than lean body mass and have body fat redistribution, such as a higher waist-to-hip circumference ratio and visceral adipose tissue than controls (Mayer et al., 2005). These unfavorable changes in body composition (sarcopenia) (Chang, Hsu, Wu, Huang, & Han, 2017) and fat distribution (abdominal obesity) (Hryhorczuk, Sharma, & Fulton, 2013) could be risk factors for depression. Moreover, DM increases chronic oxidative stress and inflammation, leading to sarcopenic obesity and depression (Oguntibeju, 2019).

From our stratification analyses, young adults (<65 years), men, and those with newly diagnosed type 2 diabetes had a more prominent association between body weight change and depression risk. Thus, the impact of body weight change on the incidence of depression may have been greater in these groups. Older adults generally have a higher prevalence of depression than younger adults, with a lower threshold for depression due to the reduced metabolism of serotonin and noradrenaline (Gottfries, 1998). A higher susceptibility to depression among women than men due to biological differences, such as estrogen cycling, could be a reason for the higher prevalence of depression among women (Albert, 2015). Such high vulnerability to depression among older adults and women might mitigate the differences in the risk of depression based on body weight changes. Regarding the duration of type 2 diabetes, taking antidiabetic agents for a longer duration may partially attenuate the magnitude of the association between body weight change and depression. Previous studies have reported that antidiabetic agents, particularly metformin, which is widely used as the first choice of treatment for type 2 diabetes, can prevent depression through neuroprotective effects (Guo et al., 2014). Furthermore, certain classes of antidiabetic medication may cause weight changes. Thus, those taking antidiabetic agents for longer durations may have a less pronounced relationship between weight change and depression.

The American Diabetes Association and the United States Preventive Services Task Force strongly recommend routine screening for depression and diabetes-related distress in adults with type 2 diabetes, because the co-existence of diabetes and depression can lead to inadequate diabetes control (Owens-Gary

et al., 2019). Our findings suggest a strategy from the viewpoint of risk stratification for depression incidence; therefore, we can intensively apply screening tools for depression in patients with type 2 diabetes who experience weight gain or loss during their regular visits.

This study has several limitations. First, we used nationwide claims data; thus, we could not distinguish between intentional and unintentional weight change. However, both intentional and unintentional weight loss were associated with depressive symptoms. However, further studies are required to clarify this relationship. Second, reverse causality could exist, although we excluded depression incidence before follow-up and applied a lag-time analysis to minimize this possibility. The average time from depression onset to the first treatment was 3.4 years in Korea. Thus, early or ongoing depressive symptoms may affect body weight. Third, the generalizability to other ethnic groups and the lowest-income groups is limited. In contrast to other ethnic/racial groups, patients with non-obese type 2 diabetes with low insulin secretion capacity are more common in the Korean population. We did not include individuals in the lowest 3% income bracket who were supported by medical aid programs. However, the population in this low-income group was relatively small and did not have a different association from the main findings. Fourth, patients with depressive symptoms might have low adherence to regular follow-up visits as well as national health check-ups; therefore, they are more likely to be excluded from this study population. However, when we compared the risk of depression between those who were included and excluded, there was a small difference in the incidence rate (32.0 *v.* 32.5 per 1000 person-years, *p-value* <0.001). Furthermore, our analysis revealed a notable difference between the included and excluded populations, particularly in terms of sex distribution, indicating a potential presence of selection bias. Finally, the absence of data regarding the use of psychotropic medication limited our analysis, despite acknowledging their impact on weight changes through metabolic aberrations.

Conclusions

A U-shaped association between body weight change and risk of depression was observed in this large nationwide cohort study. This suggests that healthcare providers should prioritize patients with type 2 diabetes and weight change (gain or loss) for depression screening to improve their health status.

References

Albert, P. R. (2015). Why is depression more prevalent in women? *Journal of Psychiatry Neuroscience*, *40*(4), 219–221. doi:10.1503/jpn.150205

An, J. H., Han, K. D., Jung, J. H., Yoo, J., Fava, M., Mischoulon, D., … Jeon, H. J. (2021). High bodyweight variability increases depression risk in patients with type 2 diabetes mellitus: A nationwide cohort study in Korea. *Frontiers in Psychiatry*, *12*, 765129. doi:10.3389/fpsyt.2021.765129

Anderson, R. J., Freedland, K. E., Clouse, R. E., & Lustman, P. J. (2001). The prevalence of comorbid depression in adults with diabetes: A meta-analysis. *Diabetes Care*, *24*(6), 1069–1078. doi:10.2337/diacare.24.6.1069

Austin, P. C. (2009). Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Statistics in Medicine*, *28*(25), 3083–3107. doi:10.1002/sim.3697

Barinas-Mitchell, E., Cushman, M., Meilahn, E. N., Tracy, R. P., & Kuller, L. H. (2001). Serum levels of C-reactive protein are associated with obesity, weight gain, and hormone replacement therapy in healthy postmenopausal women. *American Journal of Epidemiology*, *153*(11), 1094–1101. doi:10.1093/aje/153.11.1094

Barzilay, J. I., Forsberg, C., Heckbert, S. R., Cushman, M., & Newman, A. B. (2006). The association of markers of inflammation with weight change in older adults: The Cardiovascular Health Study. *International Journal of Obesity* (*Lond*), *30*(9), 1362–1367. doi:10.1038/sj.ijo.0803306

Bayani, M. A., Shakiba, N., Bijani, A., & Moudi, S. (2022). Depression and quality of life in patients with type 2 diabetes mellitus. *Caspian Journal of Internal Medicine*, *13*(2), 335–342. doi:10.22088/cjim.13.2.3

Black, S. A., Markides, K. S., & Ray, L. A. (2003). Depression predicts increased incidence of adverse health outcomes in older Mexican Americans with type 2 diabetes. *Diabetes Care*, *26*(10), 2822–2828. doi:10.2337/diacare.26.10.2822

Carvalho, L. A., Urbanova, L., Hamer, M., Hackett, R. A., Lazzarino, A. I., & Steptoe, A. (2015). Blunted glucocorticoid and mineralocorticoid sensitivity to stress in people with diabetes. *Psychoneuroendocrinology*, *51*, 209–218. doi:10.1016/j.psyneuen.2014.09.023

Cava, E., Yeat, N. C., & Mittendorfer, B. (2017). Preserving healthy muscle during weight loss. *Advances in Nutrition*, *8*(3), 511–519. doi:https://doi.org/10.3945/an.116.014506

Chang, K.-V., Hsu, T.-H., Wu, W.-T., Huang, K.-C., & Han, D.-S. (2017). Is sarcopenia associated with depression? A systematic review and meta-analysis of observational studies. *Age and Ageing*, *46*(5), 738–746. doi:10.1093/ageing/afx094

Cheol Seong, S., Kim, Y. Y., Khang, Y. H., Heon Park, J., Kang, H. J., Lee, H., … Ae Shin, S. (2017). Data resource profile: The national health information database of the national health insurance service in South Korea. *International Journal of Epidemiology*, *46*(3), 799–800. doi:10.1093/ije/dyw253

Choi, H. S., Kim, B., Han, K. D., Oh, T. R., Suh, S. H., Kim, M., … Kim, S. W. (2023). Weight change and risk of depression in patients with diabetic kidney disease: A nationwide population-based study. *Kidney Research and Clinical Practice*, *42*(1), 86–97. doi:10.23876/j.krcp.21.294

Committee, A. D. A. P. P. (2021). 8. Obesity and weight management for the prevention and treatment of type 2 diabetes: Standards of medical care in diabetes—2022. *Diabetes Care*, *45*(Supplement_1), S113-S124. doi:10.2337/dc22-S008

de Wit, L. M., van Straten, A., van Herten, M., Penninx, B. W., & Cuijpers, P. (2009). Depression and body mass index, a u-shaped association. *BMC Public Health*, 9, 14. doi:10.1186/1471-2458-9-14

Gonzalez, J. S., Safren, S. A., Cagliero, E., Wexler, D. J., Delahanty, L., Wittenberg, E., … Grant, R. W. (2007). Depression, self-care, and medication adherence in type 2 diabetes: Relationships across the full range of symptom severity. *Diabetes Care*, 30(9), 2222–2227. doi:10.2337/dc07-0158

Gottfries, C. G. (1998). Is there a difference between elderly and younger patients with regard to the symptomatology and aetiology of depression? *International Clinical Psychopharmacology*, 13(Suppl 5), S13–S18. doi:10.1097/00004850-199809005-00004

Guo, M., Mi, J., Jiang, Q. M., Xu, J. M., Tang, Y. Y., Tian, G., & Wang, B. (2014). Metformin may produce antidepressant effects through improvement of cognitive function among depressed patients with diabetes mellitus. *Clinical and Experimental Pharmacology & Physiology*, 41(9), 650–656. doi:10.1111/1440-1681.12265

Hamer, M., Batty, G. D., & Kivimaki, M. (2012). Risk of future depression in people who are obese but metabolically healthy: The English longitudinal study of ageing. *Molecular Psychiatry*, 17(9), 940–945. doi:10.1038/mp.2012.30

Hryhorczuk, C., Sharma, S., & Fulton, S. (2013). Metabolic disturbances connecting obesity and depression. *Frontiers in Neuroscience*, 7, 177. doi:10.3389/fnins.2013.00177

Jeong, S.-M., Lee, H. R., Han, K., Jeon, K. H., Kim, D., Yoo, J. E., … Shin, D. W. (2022). Association of change in alcohol consumption with risk of ischemic stroke. *Stroke*, 53(8), 2488–2496. doi:10.1161/STROKEAHA.121.037590

Jin, E. H., Han, K., Lee, D. H., Shin, C. M., Lim, J. H., Yoon, H., & Kim, N. (2021). Increased risk of major depressive disorder after cholecystectomy: A nationwide population-based cohort study in Korea. *Clinical and Translational Gastroenterology*, 12(4), e00339. doi:10.14309/ctg.0000000000000339

Jung, S. J., Woo, H. T., Cho, S., Park, K., Jeong, S., Lee, Y. J., … Shin, A. (2017). Association between body size, weight change and depression: Systematic review and meta-analysis. *The British Journal of Psychiatry*, 211(1), 14–21. doi:10.1192/bjp.bp.116.186726

Kim, M. K., Han, K., Park, Y.-M., Kwon, H.-S., Kang, G., Yoon, K.-H., & Lee, S.-H. (2018). Associations of variability in blood pressure, glucose and cholesterol concentrations, and body mass index with mortality and cardiovascular outcomes in the general population. *Circulation*, 138(23), 2627–2637. doi:10.1161/CIRCULATIONAHA.118.034978

Kim, Y. H., Han, K. D., Jung, J. H., Yoo, S. J., Lee, S. S., Lee, W. Y., … Kim, S. M. (2022). Weight change and the incidence of heart failure in the Korean population: Data from the National Health Insurance Health checkup 2005-2015. *European Journal of Preventive Cardiology*, 28(16), 1767–1773. doi:10.1093/eurjpc/zwaa049

Lustman, P. J., Anderson, R. J., Freedland, K. E., de Groot, M., Carney, R. M., & Clouse, R. E. (2000). Depression and poor glycemic control: A meta-analytic review of the literature. *Diabetes Care*, 23(7), 934–942. doi:10.2337/diacare.23.7.934

Malhi, G. S., & Mann, J. J. (2018). Depression. *The Lancet*, 392(10161), 2299–2312. https://doi.org/10.1016/S0140-6736(18)31948-2

Mathers, C. D., & Loncar, D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine*, 3(11), e442. doi:10.1371/journal.pmed.0030442

Mayer, L., Walsh, B. T., Pierson, R. N., Heymsfield, S. B., Gallagher, D., Wang, J., … Glasofer, D. (2005). Body fat redistribution after weight gain in women with anorexia nervosa 1–32. *The American Journal of Clinical Nutrition*, 81(6), 1286–1291. doi:https://doi.org/10.1093/ajcn/81.6.1286

Meurs, M., Roest, A. M., Wolffenbuttel, B. H., Stolk, R. P., de Jonge, P., & Rosmalen, J. G. (2016). Association of depressive and anxiety disorders with diagnosed versus undiagnosed diabetes: An epidemiological study of 90686 participants. *Psychosomatic Medicine*, 78(2), 233–241. doi:10.1097/psy.0000000000000255

Milaneschi, Y., Lamers, F., Berk, M., & Penninx, B. W. J. H. (2020). Depression heterogeneity and its biological underpinnings: Toward immunometabolic depression. *Biological Psychiatry*, 88(5), 369–380. doi:https://doi.org/10.1016/j.biopsych.2020.01.014

Oguntibeju, O. O. (2019). Type 2 diabetes mellitus, oxidative stress and inflammation: Examining the links. *International Journal of Physiology, Pathophysiology and Pharmacology*, 11(3), 45.

Ong, K. L., Stafford, L. K., McLaughlin, S. A., Boyko, E. J., Vollset, S. E., Smith, A. E., … Vos, T. (2023). Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: A systematic analysis for the Global Burden of Disease Study 2021. *The Lancet*, 402 (10397), 203–234. doi:10.1016/S0140-6736(23)01301-6

Owens-Gary, M. D., Zhang, X., Jawanda, S., Bullard, K. M., Allweiss, P., & Smith, B. D. (2019). The importance of addressing depression and diabetes distress in adults with type 2 diabetes. *Journal of General Internal Medicine*, 34(2), 320–324. doi:10.1007/s11606-018-4705-2

Pan, A., Sun, Q., Czernichow, S., Kivimaki, M., Okereke, O. I., Lucas, M., … Hu, F. B. (2012). Bidirectional association between depression and obesity in middle-aged and older women. *International Journal of Obesity* (Lond), 36(4), 595–602. doi:10.1038/ijo.2011.111

Penninx, B. W. J. H., Milaneschi, Y., Lamers, F., & Vogelzangs, N. (2013). Understanding the somatic consequences of depression: Biological mechanisms and the role of depression symptom profile. *BMC Medicine*, 11(1), 129. doi:10.1186/1741-7015-11-129

Perquier, F., Lasfargues, A., Mesrine, S., Clavel-Chapelon, F., & Fagherazzi, G. (2014). Body-size throughout life and risk of depression in postmenopausal women: Findings from the E3N cohort. *Obesity* (Silver Spring), 22(8), 1926–1934. doi:10.1002/oby.20799

Raison, C. L., Woolwine, B. J., Demetrashvili, M. F., Borisov, A. S., Weinreib, R., Staab, J. P., … Miller, A. H. (2007). Paroxetine for prevention of depressive symptoms induced by interferon-alpha and ribavirin for hepatitis C. *Alimentary Pharmacology & Therapeutics*, 25(10), 1163–1174. doi:10.1111/j.1365-2036.2007.03316.x

Schorr, M., Lawson, E. A., Dichtel, L. E., Klibanski, A., & Miller, K. K. (2015). Cortisol measures across the weight spectrum. *The Journal of Clinical Endocrinology and Metabolism*, 100(9), 3313–3321. doi:10.1210/jc.2015-2078

Singh, G., Jackson, C. A., Dobson, A., & Mishra, G. D. (2014). Bidirectional association between weight change and depression in mid-aged women: A population-based longitudinal study. *International Journal of Obesity* (Lond), 38(4), 591–596. doi:10.1038/ijo.2013.127

Son, K. Y., Kwon, H., Park, J. H., Joh, H. K., Hwang, S. E., Cho, S. H., … Park, Y. G. (2020). Association between weight change over a period of 4 years and mortality in Korean older adults. *Geriatrics & Gerontology International*, 20(5), 474–481. doi:10.1111/ggi.13908

Zhang, L., Li, J. L., Guo, L. L., Xu, G., Yang, L., Wang, C., … Liu, H. (2022). Weight changes and the incidence of depressive symptom in the middle-aged and older adults: Findings from the Chinese nationwide cohort study. *BMC Public Health*, 22(1), 2282. doi:10.1186/s12889-022-14624-5

Zheng, Y., Ley, S. H., & Hu, F. B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature Reviews Endocrinology*, 14(2), 88–98. doi:10.1038/nrendo.2017.151