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Bidirectional Associations Between Mental Health Disorders and Chronic Diabetic Complications in Individuals With Type 1 or Type 2 Diabetes

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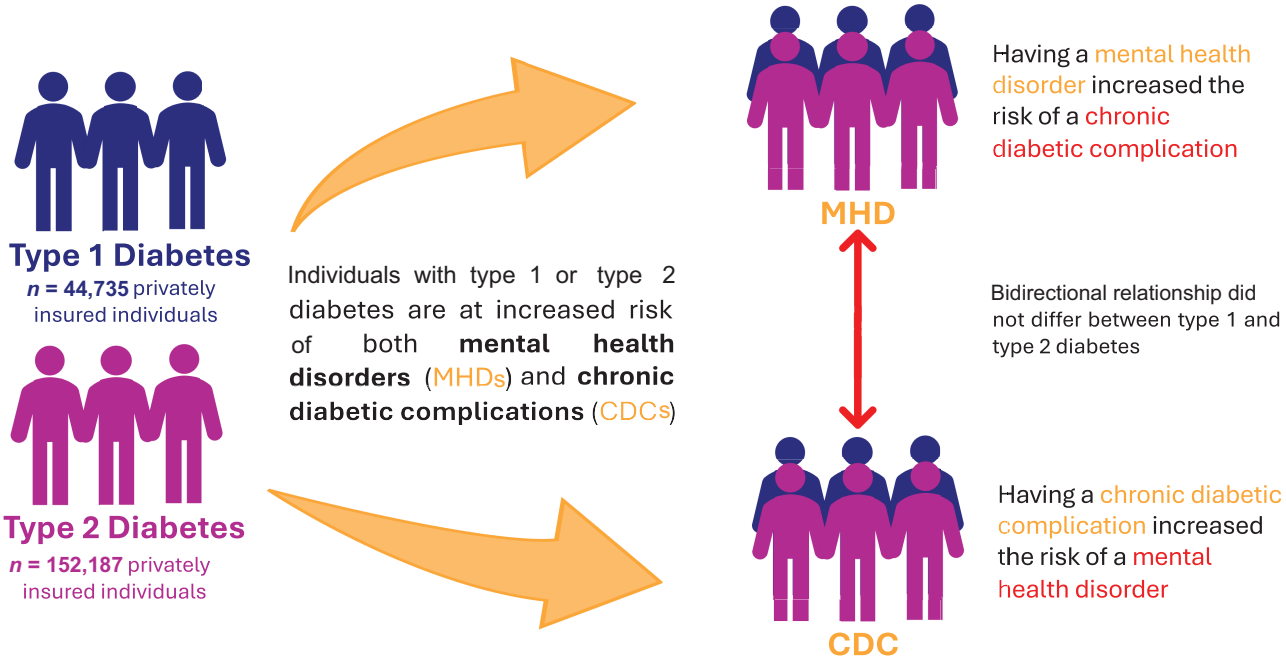
Consistent bidirectional association between mental health disorders and chronic diabetic complications in individuals with type 1 or type 2 diabetes



ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  To understand whether mental health disorders (MHDs) lead to chronic diabetes complications (CDCs) or whether CDCs lead to MHDs in individuals with type 1 or type 2 diabetes.
- **What is the specific question(s) we wanted to answer?**
  What are the bidirectional associations between the timing of MHDs and CDCs in individuals with type 1 or type 2 diabetes?
- **What did we find?**
  We found a consistent and statistically significant bidirectional relationship between MHDs and CDCs in individuals with diabetes, indicating that both comorbidities are risk factors for each other.
- **What are the implications of our findings?**
  Our results highlight the importance of screening for, treating, and preventing both MHDs and CDCs to prevent the onset of the other comorbidity.

Bidirectional Associations Between Mental Health Disorders and Chronic Diabetic Complications in Individuals With Type 1 or Type 2 Diabetes

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ORIGINAL ARTICLE

OBJECTIVE

To determine bidirectional associations between the timing of chronic diabetes complications (CDCs) and mental health disorders (MHDs) in individuals with type 1 or type 2 diabetes.

RESEARCH DESIGN AND METHODS

We used a nationally representative health care claims database to identify matched individuals with type 1 or 2 diabetes or without diabetes using a propensity score quasirandomization technique stratified by age (0–19, 20–39, 40–59, and ≥60 years). CDCs and MHDs were identified using ICD-9/10 codes. We fit Cox proportional hazards models with time-varying diagnoses of CDCs or MHDs to investigate their association with the hazard of developing MHDs or CDCs, respectively.

RESULTS

From 2001 to 2018, a total of 553,552 individuals were included (44,735 with type 1 diabetes, 152,187 with type 2 diabetes, and 356,630 without diabetes). We found that having a CDC increased the hazard of developing an MHD (hazard ratio [HR] 1.9–2.9; $P < 0.05$, with higher HRs in older age strata), and having an MHD increased the hazard of developing a CDC (HR 1.4–2.5; $P < 0.05$, with the highest HR in age stratum 0–19 years). In those aged <60 years, individuals with type 1 diabetes were more likely to have CDCs, whereas individuals with type 2 diabetes were more likely to have MHDs. However, the relationship between CDCs and MHDs in either direction was not affected by diabetes type ($P > 0.05$ for interaction effects).

CONCLUSIONS

We found a consistent bidirectional association between CDCs and MHDs across the life span, highlighting the important relationship between CDCs and MHDs. Prevention and treatment of either comorbidity may help reduce the risk of developing the other.

Individuals with diabetes are at increased risk of developing chronic complications such as neuropathy, retinopathy, diabetic kidney disease, myocardial infarction, heart failure, stroke, and peripheral vascular disease (1–4). In addition, recent meta-analyses have found that individuals with diabetes have an increased prevalence of mental

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health disorders (MHDs), including depression and anxiety (5,6). Although diabetes leads to both chronic diabetes complications (CDCs) and MHDs, the relative timing of these diabetes-related comorbidities is not well established. Understanding their timing would improve screening guidelines and the standards recommended for diabetes care and could expedite care for individuals with diabetes.

Although a few studies have identified associations between CDCs and MHDs, there is limited evidence regarding the directionality of these associations. Our recent analysis that included >1.2 million privately insured individuals found that having a CDC increased the odds of developing an MHD in both type 1 diabetes and type 2 diabetes (7). Additionally, one meta-analysis found that individuals with type 1 or 2 diabetes and depression had an increased risk of developing a CDC, perhaps because depression is associated with lower adherence to respective management plans, worsened glycemic control, increased insulin resistance, and weight gain (8). Another found significant increases in cardiovascular mortality and stroke risks in individuals with diabetes and depression (9). However, only one systematic review and meta-analysis has evaluated the bidirectional association between CDCs and depression (10). This analysis identified 16 studies that evaluated the association between baseline depression and CDCs and six that examined the reverse. Importantly, none of these studies examined both directions within the same population, and none used time-varying covariates to adjust for the relative timing of the conditions. Furthermore, although there are studies investigating the associations between MHDs and CDCs, most have focused on associations with depression and not anxiety.

Our objective was to quantify the relative timing and directionality of the associations between MHDs and CDCs in individuals with type 1 or 2 diabetes. We leveraged a large nationally representative database of privately insured individuals in the U.S. and used time-varying covariates to allow full use of the relative timing of MHDs and CDCs to investigate the bidirectional nature of the associations between the two conditions. Furthermore, we examined potential differences in the associations between these diabetes-related comorbidities between individuals with type 1 diabetes and those with type 2 and across the life span.

RESEARCH DESIGN AND METHODS

Population

We leveraged deidentified health insurance claims from Optum's Clinformatics Data Mart Database from 2001 to 2018. We used validated ICD-9 and -10 code definitions to identify individuals with type 1 diabetes (250.x1, 250.x3, E10.xx) and individuals with type 2 diabetes (250.x0, 250.x2, E11.xx) (11). For individuals with both type 1 and 2 diabetes diagnosis codes, diabetes status was determined as the diabetes type with >50% of the relevant codes (11). This definition has a sensitivity of 63% and positive predictive value of 94% for identifying individuals with type 1 diabetes and a sensitivity of 100% and positive predictive value of 90% for identifying individuals with type 2 diabetes (7). We used a simple random sample of 20% of the study population without type 1 or 2 diabetes ICD-9/10 codes as a control population without diabetes.

The University of Michigan Institutional Review Board determined that this study was exempt from ethics approval and participant consent requirements.

Matching

Our population follows from our previous study (7), which used common-referent group propensity scoring to match individuals with type 1 diabetes to individuals with type 2 diabetes and individuals without diabetes. Matching was stratified by age-group (0–19, 20–39, 40–59, and ≥60 years) and required that propensity scores be within a caliper of 0.1 for individuals aged 0–19 years and within 0.01 for individuals aged >20 years (12). Propensity scores were calculated using age at study entry, sex, race/ethnicity, geographic region, education level, net worth, insurance plan type, high-deductible health plan status, modified Charlson comorbidity index, starting year of enrollment, and length of follow-up (7). Individuals with type 1 diabetes were also matched with individuals with type 2 diabetes based on length of follow-up before diabetes diagnosis and post–diabetes diagnosis enrollment period. Based on the availability of well-matched individuals with type 2 diabetes and individuals without diabetes, for age strata 0–19 and 20–39 years, one individual with type 1 diabetes was matched to one individual with type 2 diabetes and one individual without diabetes. For age strata 40–59 and ≥60 years, one individual with type 1 diabetes was matched to four individuals with type 2 diabetes and four individuals without diabetes. Individuals with an MHD or CDC before or on the same date as diabetes diagnosis were excluded from the study.

MHDs

The timing and presence of MHDs were defined using ICD-9/10 code definitions during follow-up or a matched follow-up time in individuals without diabetes. MHDs included diagnoses of anxiety (300.0x; F41.x) and depression (296.2x, 296.3x, 300.4, 311.x; F32–34.x, F39.x). For individuals with diagnoses of both anxiety and depression, the first diagnosis date was used.

CDCs

The timing and presence of CDCs were identified using ICD-9/10 code definitions during follow-up. Complications included neuropathy (356.x, 357.1–8, 357.82, 357.89, 357.9; G60.x, G62.x, G63.x, G65.2, E08.42, E09.42, E10.42, E11.42, E13.42), retinopathy (362.0, 362.01–06, 362.0; E11.31x–E11.35x, E10.31x–E10.35x, E08.31x–E08.35x, E09.31x–E09.35x, E13.31x–E13.35x), nephropathy/diabetic kidney disease (250.4x, 585.x; E08.2x, E09.2x, E10.2x, E11.2x, E13.2x, N18.x), stroke (433.x1, 434.x1; I63.x), myocardial infarction (410.x; I21.x), and peripheral vascular disease (440.2–4, 440.9, 443.8, 443.89, 443.9, 250.7x; I70.2x–7x, I70.91–92, I73.x, I73.8, I73.89, I73.9, E08.5x, E09.5x, E10.5x, E11.5x, E13.5x) (13–16). Amputation was identified using ICD-9 procedure codes (84.11–17) and Current Procedure Terminology codes (28800, 28805, 28810, 28820, 28825). When individuals had two or more CDC diagnoses, the first diagnosis date was used.

Statistical Analysis

Descriptive statistics were used to characterize the matched individuals stratified by age-group. Pearson χ^2 tests determined associations between age-group and proportion of individuals who were diagnosed with an MHD before a CDC and, similarly, between age-group and proportion of individuals who were diagnosed with a CDC before an MHD within each diabetes group. Additionally, to determine whether diabetes type was associated

with the order in which individuals developed MHDs and CDCs, stratified by age, we performed a Cochran-Mantel-Haenszel χ^2 test. Finally, we performed Cochrane-Armitage tests for trend in proportions to determine if there were linear trends in the order of diagnoses by age within each diabetes group.

We fit Cox proportional hazards models to determine the effect of a time-varying CDC diagnosis, diabetes status (type 1 or 2 diabetes or no diabetes), and an interaction between the two on the hazard of developing an MHD for each age stratum separately. Similarly, we fit Cox proportional hazards models to determine the effect of a time-varying MHD diagnosis, diabetes status, and an interaction between the two on the hazard of developing a CDC for each age stratum separately. We censored analyses at the 90th percentile of follow-up to mitigate the effect of outliers. Scaled Schoenfeld residual plots were used to confirm the proportional hazards assumptions of our models.

Data management and analysis were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 4.2.1 (R Core Team 2022).

Data and Resource Availability

Optum's deidentified Clinformatics Data Mart Database is commercially available.

RESULTS

Study Population

The demographic, socioeconomic, and insurance plan characteristics of the individuals included in this study are listed in Table 1. We included 44,735 individuals

Table 1—Demographics of matched cohort stratified by age and diabetes type

Variable	Type 1 diabetes (*n* = 44,735)	Type 2 diabetes (*n* = 152,187)	No diabetes (*n* = 356,630)
Age stratum, years			
0–19	6,467 (14.5)	6,185 (4.1)	11,884 (3.3)
20–39	13,986 (31.3)	17,178 (11.3)	44,155 (12.4)
40–59	14,923 (33.4)	80,060 (52.6)	176,817 (49.6)
≥60	9,359 (20.9)	48,764 (32.0)	123,774 (34.7)
Sex			
Female	21,253 (47.5)	70,005 (46.0)	184,827 (51.8)
Race			
Asian	1,770 (4.0)	5,201 (3.4)	10,407 (2.9)
Black	4,900 (11.0)	16,725 (11.0)	40,386 (11.3)
Hispanic	4,909 (11.0)	13,848 (9.1)	32,316 (9.1)
White	33,156 (74.1)	116,413 (76.5)	273,521 (76.7)
Education level			
Less than 12th grade	443 (1.0)	1,331 (0.9)	3,607 (1.0)
High school diploma	12,750 (28.5)	44,218 (29.1)	112,207 (31.5)
Less than bachelor's degree	23,072 (51.6)	78,442 (51.5)	180,887 (50.7)
Bachelor's degree or higher	8,470 (18.9)	28,196 (18.5)	59,929 (16.8)
Net worth, $			
<25K	9,191 (20.6)	24,062 (15.8)	70,124 (19.7)
25K–149K	10,184 (22.8)	31,927 (21.0)	80,193 (22.5)
150K–249K	5,828 (13.0)	20,614 (13.6)	49,164 (13.8)
250K–499K	8,860 (19.8)	33,749 (22.2)	74,143 (20.8)
≥500K	10,672 (23.9)	41,835 (27.5)	83,006 (23.3)
Insurance provider			
Exclusive provider organization	4,929 (11.0)	14,523 (9.5)	29,601 (8.3)
Health maintenance organization	11,412 (25.5)	42,705 (28.1)	97,340 (27.3)
Indemnity	365 (0.8)	2,317 (1.5)	4,533 (1.3)
Other	2,483 (5.6)	11,709 (7.7)	36,637 (10.3)
Point of service	19,364 (43.3)	58,263 (38.3)	145,055 (40.7)
Preferred provider organization	6,182 (13.8)	22,670 (14.9)	43,464 (12.2)
Customer-driven health plan type			
Heath reimbursement arrangement	1,362 (3.0)	4,133 (2.7)	11,358 (3.2)
Health savings account	2,499 (5.6)	6,714 (4.4)	20,239 (5.7)
CDC	6,710 (15.0)	21,922 (14.4)	34,130 (9.6)
MHD	4,156 (9.3)	14,838 (9.8)	37,284 (10.5)
CDC and MHD	1,348 (3.0)	4,566 (3.0)	9,649 (2.7)
Microvascular/macrovascular complication first	726 (53.9)	2,358 (51.6)	4,627 (48.0)
MHD first	571 (42.4)	1,977 (43.3)	4,265 (44.2)
Tie	51 (3.8)	231 (5.1)	757 (7.9)

Data are presented as *n* (%).

with type 1 diabetes and 152,187 individuals with type 2 diabetes who did not have an MHD or CDC before or on the same date as diabetes diagnosis and 356,630 individuals with no diabetes. Characteristics of individuals were closely matched across the three groups. The proportion of female participants was well represented in each diabetes group, with 47.5%, 46.0%, and 51.8% for type 1, type 2, and no diabetes groups, respectively. A majority of each group, 74.1%, 76.5%, and 76.7%, respectively, identified as White.

The distributions of CDCs differed by diabetes status and increased by age-group. In those with type 1 diabetes, 0.8%, 3.1%, 5.2%, and 5.9% had at least one CDC for age strata 0–19, 20–39, 40–59, and ≥60 years, respectively. In individuals with type 2 diabetes, 0.1%, 0,5%, 5.8%, and 8.1% had CDCs for age strata 0–19, 20–39, 40–59, and ≥60 years, respectively. In individuals without diabetes, 0.02%, 0.2%, 2.4%, and 7.0% had CDCs for age strata 0–19, 20–39, 40–59, and ≥60 years, respectively. Across diabetes status, the distributions of MHDs increased from age-group 0–19 to 40–59 years but decreased in those aged ≥60 years. In those with type 1 diabetes, 1.2%, 2.7%, 3.2%, and 2.3% had MHDs for age strata 0–19, 20–39, 40–59, and ≥60 years, respectively. In those with type 2 diabetes, 0.4%, 1.2%, 5.1%, and 3.1% had MHDs for age strata 0–19, 20–39, 40–59, and ≥60 years, respectively. Finally, in individuals with no diabetes, 0.2%, 1.1%, 5.2%, and 3.9% had MHDs for age strata 0–19, 20–39, 40–59, and ≥60 years, respectively.

Prevalence and Timing of MHD and CDC Diagnoses

The proportions of individuals who had MHDs preceding CDCs and CDCs preceding MHDs were stratified by diabetes type and age-group. Ties were defined as diagnoses occurring on the same day. For all three groups, as age increased, the proportion of individuals who had a CDC preceding a an MHD increased (Cochrane-Armitage test for trend in proportions $P < 0.001$). In those with type 1 diabetes, the proportion of individuals diagnosed with a CDC before an MHD was not significantly different from the proportion with an MHD diagnosed before a CDC (ages 0–19 50.6% vs. 48.2%; 20–39 52.1% vs. 44.4%; 40–59 52.5% vs. 43.8%; ≥60 years 56.2% vs. 39.5%; all Pearson χ^2 test $P > 0.05$). Similarly, in those with type 2 diabetes, the proportion of individuals diagnosed with a CDC before an MHD was not significantly different from the proportion with an MHD diagnosed before a CDC (ages 0–19 62.5% vs. 37.5%; 20–39 48.2% vs. 47.0%; 40–59 43.7% vs. 51.7%; ≥60 years 54.6% vs. 40.1%; all Pearson χ^2 test $P > 0.05$).

Time-Varying Covariate Cox Regression Models

The hazard ratio (HR) estimates and corresponding 95% Wald CIs for model covariates stratified by age-group for time to an MHD and time to a CDC are listed in Table 2.

Time to an MHD Diagnosis

The presence of a CDC increased the risk of developing an MHD across the life span (ages 0–19 HR 2.1 [95% CI 1.4–3.2]; 20–39 HR 1.9 [95% CI 1.6–2.4]; 40–59 HR 2.1 [95% CI 1.8–2.5]; ≥60 years HR 2.9 [95% CI 2.4–3.4]), with the highest risk seen in the oldest age-group (Fig. 1*A*–*D*).

Individuals with type 2 diabetes had a significantly increased risk of developing an MHD compared with individuals with type 1 diabetes in all age-groups except for those aged ≥60 years (ages 0–19 HR 1.3 [95% CI 1.2–1.5]; 20–39 HR 1.4 [95% CI 1.3–1.5]; 40–59 HR 1.2 [95% CI 1.1–1.3]; ≥60 years HR 1.0 [95% CI 0.9–1.1]). Compared with those with type 1 diabetes, individuals without diabetes had a significantly increased risk of developing an MHD in all age-groups except those aged 0–19 years (ages 0–19 HR 1.0 [95% CI 0.9–1.2]; 20–39 HR 1.4

Table 2—HRs of Cox regression models with time-varying covariates for CDC or MHD, diabetes status, and interactions

	Time to MHD		Time to CDC	
Age-group, years	Parameter	HR (95% Wald CI)	Parameter	HR (95% Wald CI)
0–19	CDC	2.1* (1.4, 3.2)	MHD	2.5* (1.7, 3.7)
	No diabetes (ref type 1)	1.0 (0.9, 1.2)	No diabetes (ref type 1)	0.1* (0.05, 0.1)
	Type 2 (ref type 1)	1.3* (1.2, 1.5)	Type 2 (ref type 1)	0.2* (0.2, 0.3)
	CDC × no diabetes	2.2 (0.9, 5.1)	MHD × no diabetes	1.1 (0.3, 3.2)
	CDC × type 2	1.3 (0.6, 2.8)	MHD × type 2	0.1 (0.3, 1.7)
20–39	CDC	1.9* (1.6, 2.4)	MHD	1.5* (1.2, 1.9)
	No diabetes (ref type 1)	1.4* (1.3, 1.5)	No diabetes (ref type 1)	0.1* (0.09, 0.1)
	Type 2 (ref type 1)	1.4* (1.3, 1.5)	Type 2 (ref type 1)	0.4* (0.3, 0.4)
	CDC × no diabetes	1.2 (0.8, 1.7)	MHD × no diabetes	2.2* (1.5, 3.1)
	CDC × type 2	1.0 (0.7, 1.4)	MHD × type 2	1.3 (0.9, 1.8)
40–59	CDC	2.1* (1.8, 2.5)	MHD	1.4* (1.2, 1.7)
	No diabetes (ref type 1)	1.4* (1.3, 1.5)	No diabetes (ref type 1)	0.3* (0.2, 0.3)
	Type 2 (ref type 1)	1.2* (1.1, 1.3)	Type 2 (ref type 1)	0.7* (0.6 0.7)
	CDC × no diabetes	1.1 (0.9, 1.3)	MHD × no diabetes	1.8* (1.5, 2.1)
	CDC × type 2	0.9 (0.7, 1.1)	MHD × type 2	1.1 (0.9, 1.3)
≥60	CDC	2.9* (2.4, 3.4)	MHD	1.6* (1.3, 1.8)
	No diabetes (ref type 1)	1.4* (1.3, 1.6)	No diabetes (ref type 1)	0.69* (0.67, 0.7)
	Type 2 (ref type 1)	1.0 (0.9, 1.1)	Type 2 (ref type 1)	1.0 (0.9, 1.01)
	CDC × no diabetes	1.1 (0.9, 1.3)	MHD × no diabetes	1.3* (1.1, 1.5)
	CDC × type 2	1.0 (0.8, 1.2)	MHD × type 2	1.1 (0.9, 1.3)

Time to MHD and time to CDC were modeled for individuals for each age-group. *$P < 0.05$.

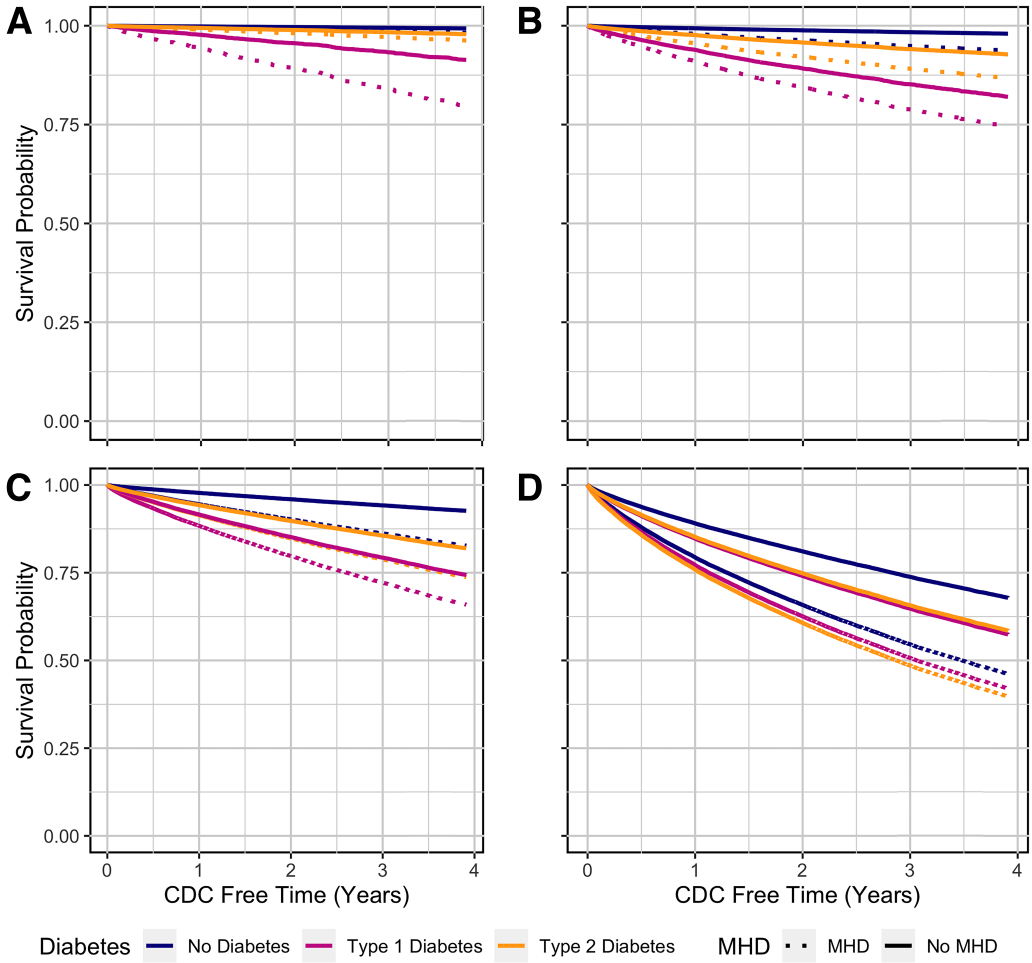

Figure 1—Estimated survival plots of Cox hazards models for time to CDC with time-varying MHD diagnosis. Plots display survival predictions for individuals with type 1 or type 2 or no diabetes with or without MHD. Age-groups are plotted as follows: 0–19 (*A*), 20–39 (*B*), 40–59 (*C*), and ≥60 (*D*) years.

[95% CI 1.3–1.5]; 40–59 HR 1.4 [95% CI 1.3–1.5]; ≥60 years HR 1.4 [95% CI 1.3–1.6]).

We found no significant differences in the effect of CDCs across diabetes status. The interaction effects between diabetes and CDCs were not statistically significant ($P > 0.05$ in all cases).

Time to a CDC Diagnosis

An MHD diagnosis significantly increased the risk of developing a CDC across age-groups (age 0–19 HR 2.5 [95% CI 1.7–3.7]; 20–39 HR 1.5 [95% CI 1.2–1.9]; 40–59 HR 1.4 [95% CI 1.2–1.7]; ≥60 years HR 1.6 [95% CI 1.3–1.8]). The magnitude of this effect decreased from age 0–19 to 20–39 years but remained relatively stable to age 40–59 and ≥60 years (Fig. 2*A*–*D*).

Individuals with type 2 diabetes and without an MHD had a significantly decreased risk of CDCs compared with those with type 1 diabetes in all age-groups except those aged ≥60 years (age 0–19 HR 0.2 [95% CI 0.2–0.3]; 20–39 HR 0.4 [95% CI 0.3–0.4]; 40–59 HR 0.7 [95% CI 0.6–0.7]; ≥60 years HR 1.0 [95% CI 0.9–1.01]). Individuals without diabetes and without an MHD had a significantly decreased hazard of CDCs compared with individuals with type 1 diabetes across all age-groups, with the magnitude decreasing across the life span (age 0–19 HR 0.1 [95% CI 0.05–0.1]; 20–39 HR 0.1 [95% CI 0.09–0.1]; 40–59 HR 0.3 [95% CI 0.2–0.3]; ≥60 years HR 0.69 [95% CI 0.67–0.7]).

We found that the effects of MHDs on the risk of CDCs did not differ between those with type 1 diabetes and those with type 2 diabetes (diabetes and MHD interaction effects $P > 0.05$). In contrast, in individuals without diabetes, the effect of an MHD on the hazard of developing a CDC was significantly greater than that in individuals with type 1 diabetes in all age strata except those aged 0–19 years, with a decreasing effect as age increased (no diabetes and MHD interaction effect age 0–19 HR 1.1 [95% CI 0.3–3.2]; 20–39 HR 2.2 [95% CI 1.5–3.1]; 40–59 HR 1.8 [95% CI 1.5–2.1]; ≥60 years HR 1.3 [95% CI 1.1–1.5]).

CONCLUSIONS

In a large well-matched cohort of privately insured individuals with type 1 or 2 diabetes or without diabetes, we found a consistent bidirectional association between CDCs and MHDs across diabetes type and the life span, indicating that an individual with one of the diabetes-related comorbidities has an increased likelihood of developing the other. Additionally, we found that the effect of a CDC on the risk of developing an MHD increased across the life span, whereas the effect of an MHD on developing a CDC remained relatively stable apart from a higher risk in those aged <20 years. Finally, in this population, we found that individuals with type 1 diabetes were more

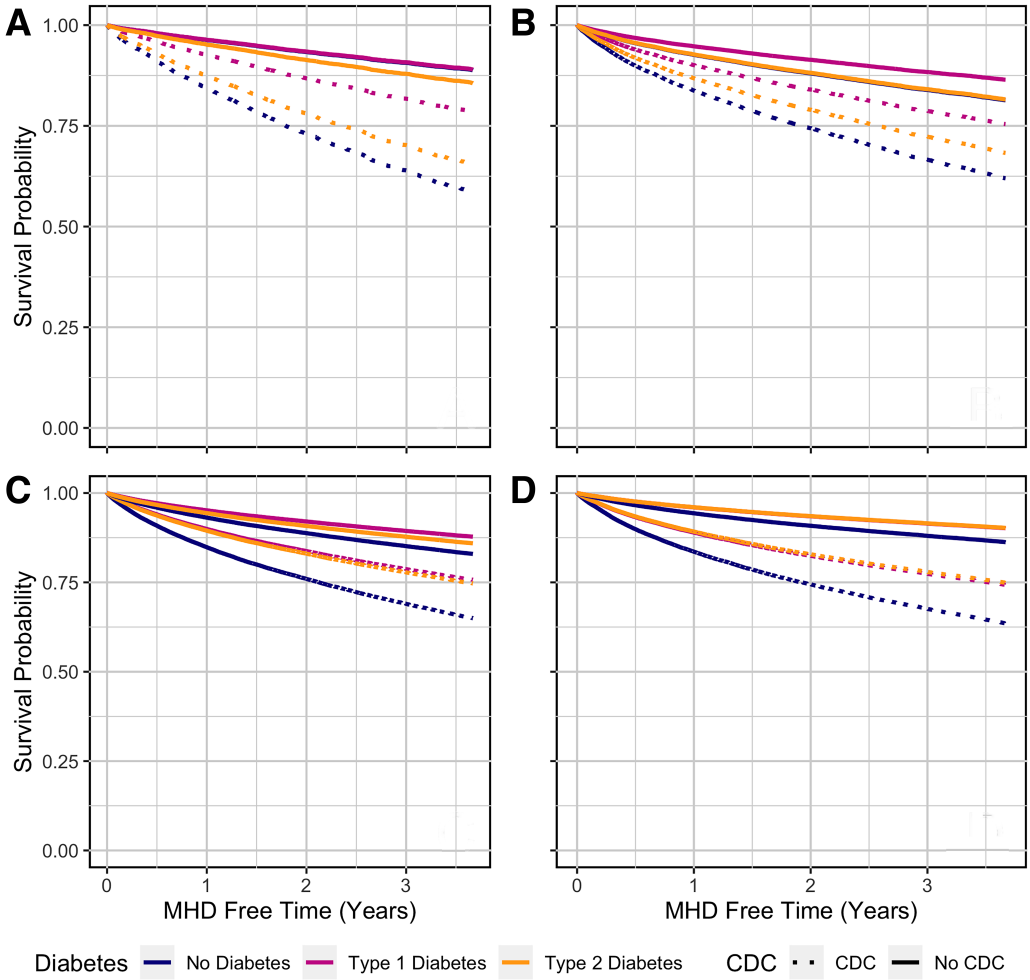

Figure 2—Estimated survival plots of Cox hazards models of time to MHD with time-varying CDC. Plots display survival predictions for individuals with type 1 or type 2 or no diabetes with or without CDC. Age-groups are plotted as follows: 0–19 (*A*), 20–39 (*B*), 40–59 (*C*), and ≥60 (*D*) years.

likely to be diagnosed with a CDC, whereas individuals with type 2 diabetes were more likely to be diagnosed with an MHD.

We found a consistent and statistically significant bidirectional relationship between CDCs and MHDs in individuals with diabetes across the life span. This bidirectional relationship did not differ between those with type 1 diabetes and those with type 2. Through this study, we attempted to understand whether MHDs lead to CDCs or whether CDCs lead to MHDs, but we found that both relationships are true. Clinically, these findings indicate that clinicians should actively screen for MHDs in individuals with diabetes in addition to screening for the traditional CDCs, which has been and is the recommended current standard of care in diabetes (17). Furthermore, these findings also imply that in addition to treating only the usual risk factors to prevent CDCs, clinicians and health care systems should revise standards of care practices to include MHD screening and treatment. A number of diabetes centers nationally (particularly those focused on type 1 diabetes) have implemented depression and distress screening for their patient populations, but active and universal screening for MHDs is needed for all patients with diabetes at the point of care (18,19). Additionally, expertise and resources are needed to screen for and manage these conditions once identified, given that many clinicians involved in the management of diabetes lack the specific training to adequately identify and treat MHDs (20). In addition, this will add burden to the already comprehensive workload of primary care providers and endocrinologists, which can negatively affect patient quality of care and costs (21). Importantly, screening for MHDs alone may increase the prevalence of these conditions but may not result in improved MHD prognosis. According to the U.S. Preventive Services Task Force guidelines on MHD screening, "adequate systems and clinical staff are needed to ensure that patients are screened and, if they screen positive, are appropriately diagnosed and treated with evidence-based care or referred to a setting that can provide the necessary care" (22,23). Therefore, when screening individuals with diabetes for MHDs, it is critical to ensure there are adequate systems in place to provide optimal care. Solutions would involve changes in health policies to ensure adequate insurance coverage for mental health services, revision of standards of care, and embedding of clinical decision support systems in electronic health records to help streamline diagnostic and treatment processes with the goal of improving patient outcomes (24); development of multidisciplinary collaborative care models to manage these wide-ranging diabetes-related comorbidities (25); and increase in access to psychiatrists and

psychologists through traditional in-person visits, telemedicine visits, electronic consultations, and/or multidisciplinary clinics.

The mechanisms underlying the bidirectional relationship between MHDs and CDCs are unclear. It is possible that developing one diabetes comorbidity has direct effects on developing another diabetes comorbidity. For instance, strokes cause detrimental effects on the brain, which may directly lead to depression (21). Alternatively, it is possible that symptoms stemming from one diabetes comorbidity may have indirect effects on the development of the other diabetes comorbidity. For example, MHDs in individuals with diabetes may affect self-management of their condition, including poor glycemic control and medication nonadherence, which in turn may increase individuals' risk of CDCs (26,27). Another explanation is that in those with diabetes, CDCs and MHDs share common risk factors (e.g., glycemic control, obesity, socioeconomic factors, treatment adherence), which might increase the likelihood of developing both comorbidities. For example, studies have shown that diabetes and obesity are major risk factors for developing neuropathy and depression (28,29). Therefore, diabetes care providers may be able to simultaneously prevent the risk of multiple complications by providing interventions that treat these shared risk factors (e.g., glucagon-like peptide 1 receptor agonists, bariatric surgery). Most likely, a combination of direct and indirect effects and shared risk factors drive associations between MHDs and CDCs and vice versa. Future studies are required to better understand the complex multifaceted associations between MHDs and CDCs in individuals with diabetes and thus inform future interventions. Because the current literature has focused on anxiety and depression in individual with diabetes, our analysis takes a narrow approach to MHDs; however, we were interested in these relationships with CDCs in general and therefore did not focus on any specific complications. Additional studies might investigate the complications included in our definition more specifically.

We found that the effect of a CDC on the hazard of an MHD increased across the life span, whereas the effect of an MHD on a CDC was relatively stable, except for larger effects in those age <20 years. One explanation for this finding is that the number and severity of CDCs increase across the life span, ultimately increasing the impact on incidence of MHDs. For example, older individuals with neuropathy often have increased pain and risk of falls and decreased mobility and quality of life (27,28). Chronic neuropathic pain can also increase the risk of depression and anxiety (30). Additionally, older adults are more likely to experience stroke, which increases the risk of disability and poor physical or cognitive function, leading to poststroke depression (31–33). On the other hand, although individuals with diabetes at both younger and older ages have an increased risk of MHDs (34,35), the health detriment resulting from those disorders, which increases individuals' risk of CDCs, likely remains relatively stable as age increases. Although preventing diabetes comorbidities across the life span will likely prevent the onset of other comorbidities, our results indicate that interventions to prevent CDCs are likely to have a particularly important role in reducing MHDs in older populations. On the other hand, given that the effect of MHDs on CDCs is highest in those aged <20 years, interventions to identify, treat, and reduce MHDs may be particularly important in younger populations. This finding emphasizes the need for mental health services and transition programs, particularly within the transition age-group (adolescents), in which patients have traditionally struggled with glycemic control (36,37). Interestingly, we also found that individuals with no diabetes had an increased risk of MHDs compared with individuals with type 1 diabetes in all except the youngest age-group. One explanation for this finding lies in the burden of care for clinicians treating individuals with diabetes. Routine screening for anxiety and depression may not take precedence if an individual with diabetes is currently undergoing treatment for concurrent CDCs; thus, diagnoses of MHDs may not be a priority. In contrast, in individuals with MHDs, there may be more bandwidth for clinicians to be screening and diagnosing MHDs.

Limitations to the current study include possible misclassifications of diabetes type, MHDs, and CDCs with the use of ICD-9/10 codes. Although many of these definitions have been validated with high positive predictive ability, misclassification is still possible. Furthermore, because our data detail only the clinically diagnosed dates of complications, we were not able to capture the presence or onset of symptoms. Even if they screen for MHDs, providers may not be confident in diagnosing a patient, or they may be reluctant to code an MHD because of concerns about insurance eligibility or stigma, both of which may lead to underreporting. Use of ICD-9/10 codes did not allow us to quantify the severity of diabetes status, MHDs, or CDCs. Therefore, we were unable to determine if more severe MHDs or CDCs increased the hazard of CDCs or MHDs, respectively. Furthermore, our definitions of MHDs and CDCs were broad and included multiple disorders. Our study lacked the detailed clinical information required to determine the mechanisms underpinning this bidirectional relationship. Therefore, to develop the optimal prevention strategies for individuals with diabetes, future studies, with detailed patient information and sensitive markers of these diabetes comorbidities, are needed to fully understand the mechanisms underlying this bidirectional relationship.

Although some of these disorders and complications are related, there may be condition-specific mechanisms that were not captured in the current study. For example, diabetes distress, a common comorbidity, is more highly associated with glycemic outcomes than depression or anxiety; however, it is not captured in the ICD-9/10 codes (38). Finally, although this claims database provides a rich resource for identifying individuals with a wide range of MHDs and CDCs, the generalizability to populations outside of the U.S. or to U.S. populations not covered by private insurance (e.g., Medicaid, Medicare, veterans) is unclear and requires further study.

In summary, we found a bidirectional association between MHDs and CDCs. That is, both comorbidities are risk factors for each other, highlighting the importance of screening for, treating, and preventing both MHDs and CDCs. Diabetes clinicians and health care systems likely need to increase their focus on MHDs, and innovative models of care are required to optimize care for both individuals with type 1 diabetes and those with type 2 diabetes. Importantly, future studies are needed to better understand the reasons for the complex bidirectional relationship between MHDs and CDCs to guide future interventions.

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Author Contributions. M.W. and E.L.R. were involved in the study design, performed the statistical analysis, and wrote the manuscript. M.B. was involved in the interpretation of the analysis and critical revisions of the manuscript. M.C. was involved in the study design, interpretation of the analysis, and critical revisions of the manuscript. K.M.-S. and D.A. were involved in the interpretation of the analysis and critical revisions of the manuscript. L.A. was involved in the critical review and revisions of the manuscript. J.M.L. was involved in the study design and critical revisions of the manuscript. R.P.-B. and E.L.F. were involved in the interpretation of the analysis and critical revisions of the manuscript. B.C.C. was involved in the study design, interpretation of the statistical analysis, and critical revisions of the manuscript. B.C.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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