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A Propensity-Matched Study of the Association of Diabetes Mellitus with Incident Heart Failure and Mortality among Community-Dwelling Older Adults

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Abstract

Diabetes mellitus (DM) is a risk factor for incident heart failure (HF) in older adults. However, to what extent this association is independent of other risk factors remains unclear. Of the 5464 community-dwelling adults ≥ 65 years in the Cardiovascular Health Study without baseline HF, 862 had DM (fasting plasma glucose levels ≥ 126 mg/dl, or treatment with insulin or oral hypoglycemic agents). Propensity scores for DM were estimated for each of the 5464 participants and were used to assemble a cohort of 717 pairs of participants with and without DM, who were balanced on 65 baseline characteristics. Incident HF occurred in 31% and 26% of matched participants with and without DM, respectively, during over 13 years of follow-up (hazard ratio {HR} when DM was compared with no DM, 1.45; 95% confidence interval {CI}, 1.14–1.86; $p=0.003$). Among the 5464 pre-match participants, unadjusted and multivariable-adjusted HRs for incident HF associated with DM were 2.22 (95% CI, 1.94–2.55; $p<0.001$) and 1.52 (95% CI, 1.30–1.78; $p<0.001$), respectively. All-cause mortality occurred in 57% and 47% of matched participants with and without DM respectively (HR, 1.35; 95% CI, 1.13–1.61; $p=0.001$). Among matched participants, DM-associated HRs for incident peripheral arterial disease, incident acute myocardial infarction and incident stroke were 2.50 (95% CI, 1.45–4.32; $p=0.001$), 1.37 (95% CI, 0.97–1.93; $p=0.072$), and 1.11 (95% CI, 0.81–1.51; $p=0.527$), respectively. In conclusion, the association of DM with incident HF and all-cause mortality in community-dwelling older adults without HF is independent of major baseline cardiovascular risk factors.

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Disclosures:

None.

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Keywords

heart failure; diabetes mellitus; mortality; older adults; propensity-matched

Diabetes mellitus (DM) is a major risk factor for incident heart failure (HF).^{1, 2} However, DM is also associated with many traditional cardiovascular risk factors.³ To what extent the association of DM with incident HF is independent of other cardiovascular risk factors remains unclear. Although traditional multivariable risk adjustment models can account for baseline differences in the distribution of such risk factors, they cannot guarantee that they would be balanced.⁴ Propensity score matching, on the other hand, can be used to for outcome-blinded assembly of study cohorts in which exposed and unexposed groups are balanced on all measured baseline characteristics.^{5–7} Therefore, we conducted a propensity-matched study of the association of DM with incident heart failure, mortality, and incident cardiovascular events.

Methods

The Cardiovascular Health Study (CHS) is a National Heart, Lung, and Blood Institute (NHLBI)-funded prospective study designed to assess the traditional and non-traditional cardiovascular risk factors among community-dwelling older adults.⁸ The CHS recruited 5888 Medicare-eligible community-dwelling adults ≥ 65 years of age from four US communities in two phases. A mostly white initial cohort of 5201 participants (1989–1990) was later supplemented by 687 African-Americans from three of those four communities (1992–1993). We used a de-identified public-use copy of the CHS dataset obtained from the NHLBI which contained information on 5795 participants who consented to be included in that dataset. After excluding 63 participants without data on DM status and 268 participants with prevalent HF at baseline, the final sample size for the current analysis was 5464 participants.

Baseline DM was defined by fasting plasma glucose (FPG) level >126 mg/dl or treatment with insulin or hypoglycemic drugs, and 16% (862/5464) of the CHS participants had DM. Data on socio-demographic, clinical, sub-clinical, and laboratory variables including serum insulin, triglyceride, interleukin-6 (IL-6), and C-reactive protein (CRP) levels were measured at baseline.⁸ If the value of a continuous variable was found to be missing, then predicted values based on age, sex and race were imputed. The primary outcome for this study was incident HF, which was centrally adjudicated by the CHS Events Committee. Data on self-reports of physician diagnosis of HF were obtained during semi-annual visits, which was then verified via review of medical records.^{2, 9, 10} Secondary outcomes included all-cause and cause-specific mortalities, acute myocardial infarction (AMI), stroke, and peripheral arterial disease (PAD).

Propensity scores, or the conditional probability of having DM, were estimated for each of the 5,464 participants using a non-parsimonious multivariable logistic regression model in which DM was the dependent variable and the 65 baseline characteristics were covariates.^{11–14} We then used the propensity scores to match 717 (83% of the 862) individuals with DM with 717 of those without DM who had similar propensity scores.^{15–18} Pre- and post-match absolute standardized differences for all 65 covariates were estimated and presented as a Love plot (Figure 1).^{19–23} An absolute standardized difference of less than 10% indicates inconsequential imbalances, while 0% indicates no between-group imbalances on that covariate.^{24, 25}

For between-group comparisons for pre- and post-match data, we used Pearson chi-square tests, Wilcoxon rank-sum tests, McNemar's tests and paired sample t-tests, as appropriate. Kaplan-Meier and matched Cox proportional hazard analyses were used to estimate the associations between DM and outcomes. Formal sensitivity analyses were conducted to determine the impact of a potential hidden confounder on the association between DM and incident HF in the matched cohort.²⁶ Subgroup analyses were performed to determine the homogeneity of this association. Two-tailed statistical tests with 95% confidence intervals were employed with a p-value <0.05 considered to be significant. All data analysis was completed using SPSS for Windows (Version 15).

Results

Our matched cohort had a mean ($\pm$ SD) age of 73 ($\pm$ 6) years, 51% were women, and 21% were African American (Table 1). Before matching, participants with DM were more likely to have a history of CAD, hypertension, stroke, and higher mean serum insulin, triglyceride, IL-6 and CRP levels. These and other imbalances were balanced in the matched cohort (Table 1 and Figure 1).

Incident HF occurred in 31% and 26% of matched participants with and without DM, respectively, during over 13 years of follow-up (hazard ratio {HR}, 1.45; 95% confidence interval {CI}, 1.14–1.86; $p=0.003$; Table 2, Figure 2). A hidden binary covariate that is a near-perfect predictor of incident HF would need to increase the odds of DM by 23% to explain away this association. This association was homogeneous across various subgroups of matched participants except that it was stronger in those without hypertension than in those with hypertension (Figure 3). Pre-match associations of DM with incident HF are displayed in Table 2.

All-cause mortality in the post-match cohort occurred in 57% and 47% of participants with and without DM, respectively (HR, 1.35; 95% CI, 1.13–1.61; $p=0.001$; Table 3, Figure 2). Associations of DM with cardiovascular and non-cardiovascular mortality are displayed in Table 3. Associations of DM with other incident cardiovascular outcomes are displayed in Table 4. Of those who developed incident HF, only 25 (8%) patients had incident AMI prior to HF, which occurred in 1% (6 of 630) and 3% (19 of 632) of those with and without DM, respectively ($p=0.009$).

Discussion

Findings from the current propensity-matched study of community-dwelling older adults demonstrate that DM had a strong association with incident HF and all-cause mortality, and these associations were independent of most traditional and non-traditional cardiovascular risk factors at baseline. The results from the current study also demonstrate that the higher incidence of HF among those with DM was in large part due to a higher incidence of AMI in those individuals. In contrast to prior studies of the association of DM and cardiovascular outcomes,^{1, 27–31} to the best of our knowledge, this is the first propensity-matched population based study of older adults that demonstrated an independent association of DM with incident HF and mortality.

The independent association of DM with incident HF and all-cause mortality observed in our propensity-matched cohort cannot be explained by any of the 65 balanced baseline characteristics. Therefore, there are two potential explanations for these associations: confounding by unmeasured covariates or a true intrinsic association. Findings from our sensitivity analysis suggest that the association of DM with incident HF is unlikely to be due to potential unmeasured confounders. Potential mechanistic explanations for an intrinsic

association include DM-associated neurohormonal activation, impaired calcium homeostasis, oxidative stress, mitochondrial dysfunction, protein kinase C activation, microangiopathy, collagen accumulation, and formation of advanced glycation end-products, all of which may lead to diabetic cardiomyopathy.^{32–36} Our findings suggest that the higher incidence of HF in those with DM was in large part due to a higher incidence of AMI in those individuals.

The confounding role of the cardiovascular risk factors and mediating role of incident AMI suggest that optimal management of cardiovascular risk factors in those with DM may play an important role in the secondary prevention of HF in community-dwelling older adults with DM. Whether a more aggressive management of DM would further reduce the risk adverse cardiovascular events remains unclear. While intensive DM management has been shown to reduce the risk of microvascular complications, it has no effect on adverse cardiovascular events,³⁷ and may even be associated with increased risk of overall mortality.³⁸ A meta-analysis of 5 prospective trials also found no evidence that more intensive glycemic control resulted in lower risk of incident HF.³⁹ Therefore, prevention efforts may need to focus on the primary prevention of DM.

Our study has several limitations. While propensity matching allowed us to balance many confounding comorbid conditions, we were not able to account for the duration, severity, or extent of many of these comorbid conditions. Additionally, we had no data on HF etiology or left ventricular systolic function for those with incident HF. It is also possible that those without DM at baseline developed DM during follow-up. This regression dilution may have underestimated the association of DM with outcomes in our study.⁴⁰ In conclusion, DM is independently associated with incident HF and all-cause mortality in community-dwelling older adults without HF.

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Figure 1.

Absolute standardized differences comparing 65 baseline characteristics between CHS participants with and without diabetes mellitus, before and after propensity score matching. (ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease; EKG = electrocardiogram; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LV = left ventricular; MMSE = Mini-Mental State Examination; NSAIDs = nonsteroidal anti-inflammatory drugs)

Figure 2. Kaplan-Meier plots for (a) incident heart failure and (b) mortality due to all causes by presence or absence of diabetes mellitus (DM) in a propensity-matched cohort of CHS participants (HR=hazard ratio; CI=confidence interval)

Figure 3. Association of diabetes mellitus (DM) with incident heart failure in subgroups of propensity-matched CHS participants (CI=confidence interval; HR=hazard ratio)

Table 1

Baseline characteristics of patients by diabetes before and after propensity matching

n (%) or mean ($\pm$ SD)	Pre-match Diabetes mellitus		P Value	Post-match Diabetes mellitus		P Value
	No (n =4602)	Yes (n =862)		No (n =717)	Yes (n =717)	
Age, years	73 ($\pm$ 6)	73 ($\pm$ 5)	0.936	73 ($\pm$ 5)	73 ($\pm$ 6)	0.646
Female	2714 (59%)	434 (50%)	<0.001	364 (51%)	367 (51%)	0.916
African American	610 (13%)	204 (24%)	<0.001	144 (20%)	159 (22%)	0.361
Body mass index (kg/m ²)	26 ($\pm$ 4)	28 ($\pm$ 4)	<0.001	28 ($\pm$ 4)	28 ($\pm$ 4)	0.409
Married	3101 (67%)	541 (63%)	0.008	463 (65%)	462 (64%)	1.000
Current smoker	580 (13%)	85 (10%)	0.024	79 (11%)	73 (10%)	0.666
Smoking (pack-years)	17 ($\pm$ 26)	20 ($\pm$ 30)	0.006	19 ($\pm$ 28)	19 ($\pm$ 28)	0.581
Alcohol intake (units/week)	3 ($\pm$ 7)	2 ($\pm$ 5)	<0.001	2 ($\pm$ 6)	2 ($\pm$ 5)	0.800
General health, fair to poor	948 (21%)	329 (38%)	<0.001	258 (36%)	247 (34%)	0.541
Past medical history						
Coronary artery disease	743 (16%)	209 (24%)	<0.001	172 (24%)	165 (23%)	0.709
Acute myocardial infarction	332 (7%)	108 (13%)	<0.001	87 (12%)	85 (12%)	0.935
Angina pectoris	617 (13%)	174 (20%)	<0.001	148 (21%)	135 (19%)	0.426
Coronary artery bypass surgery	154 (3%)	51 (6%)	<0.001	40 (6%)	38 (5%)	0.905
Hypertension	2556 (56%)	623 (72%)	<0.001	505 (70%)	506 (71%)	1.000
Chronic kidney disease	952 (21%)	190 (22%)	0.369	152 (21%)	152 (21%)	1.000
Stroke	154 (3%)	55 (6%)	<0.001	34 (5%)	39 (5%)	0.620
Transient ischemic attack	107 (2%)	34 (4%)	0.006	27 (4%)	24 (3%)	0.775
Peripheral arterial disease	511 (11%)	169 (20%)	<0.001	130 (18%)	134 (19%)	0.832
COPD	581 (13%)	95 (11%)	0.189	86 (12%)	80 (11%)	0.685
Cancer	669 (15%)	111 (13%)	0.201	93 (12%)	93 (13%)	1.000
Clinical examination						
Pulse rate (beats/min)	67 ($\pm$ 11)	71 ($\pm$ 12)	<0.001	70 ($\pm$ 11)	70 ($\pm$ 12)	0.895
Systolic BP (mmHg)	136 ($\pm$ 21)	141 ($\pm$ 21)	<0.001	140 ($\pm$ 22)	140 ($\pm$ 21)	0.990
Diastolic BP (mmHg)	71 ($\pm$ 11)	71 ($\pm$ 12)	0.631	71 ($\pm$ 11)	71 ($\pm$ 12)	0.558
Medications						
ACE inhibitor	254 (6%)	95 (11%)	<0.001	77 (11%)	74 (10%)	0.857

n (%) or mean ($\pm$ SD)	Pre-match Diabetes mellitus		P Value	Post-match Diabetes mellitus		P Value
	No (n =4602)	Yes (n =862)		No (n =717)	Yes (n =717)	
Beta blocker	553 (12%)	142 (17%)	<0.001	130 (18%)	117 (16%)	0.411
Calcium channel blocker	527 (12%)	158 (18%)	<0.001	129 (18%)	126 (18%)	0.891
Statin	94 (2%)	27 (3%)	0.046	22 (3%)	19 (3%)	0.755
Loop diuretic	183 (4%)	76 (9%)	<0.001	62 (9%)	53 (7%)	0.444
Thiazide diuretic	489 (11%)	130 (15%)	<0.001	109 (15%)	103 (14%)	0.701
Nitrate	323 (7%)	91 (11%)	<0.001	69 (10%)	73 (10%)	0.789
Digoxin	259 (6%)	101 (12%)	<0.001	59 (8%)	65 (9%)	0.631
Laboratory values						
Creatinine (mg/dl)	0.95 ($\pm$ 0.32)	1.00 ($\pm$ 0.60)	0.001	0.99 ($\pm$ 0.34)	0.99 ($\pm$ 0.64)	0.877
Potassium (mEq/L)	4.16 ($\pm$ 0.37)	4.16 ($\pm$ 0.41)	0.880	4.17 ($\pm$ 0.40)	4.16 ($\pm$ 0.40)	0.764
Cholesterol (mg/dl)	213 ($\pm$ 38)	206 ($\pm$ 42)	<0.001	205 ($\pm$ 39)	207 ($\pm$ 42)	0.398
LDL (mg/dl)	131 ($\pm$ 35)	126 ($\pm$ 38)	<0.001	126 ($\pm$ 34)	127 ($\pm$ 37)	0.574
HDL (mg/dl)	56 ($\pm$ 16)	48 ($\pm$ 13)	<0.001	48 ($\pm$ 12)	48 ($\pm$ 13)	0.468
Triglyceride (mg/dl)	133 ($\pm$ 67)	172 ($\pm$ 111)	<0.001	163 ($\pm$ 93)	163 ($\pm$ 93)	0.915
Uric acid (mg/dl)	5.6 ($\pm$ 1.5)	5.8 ($\pm$ 1.5)	0.001	5.8 ($\pm$ 1.5)	5.8 ($\pm$ 1.5)	0.868
C-reactive protein (mg/L)	4.2 ($\pm$ 7.0)	6.8 ($\pm$ 12.3)	<0.001	6.1 ($\pm$ 10.7)	5.9 ($\pm$ 8.2)	0.671
Insulin (IU/ml)	14 ($\pm$ 8)	32 ($\pm$ 56)	<0.001	20 ($\pm$ 15)	20 ($\pm$ 13)	0.879
Interleukin-6 (pg/ml)	2.1 ($\pm$ 1.8)	2.6 ($\pm$ 1.7)	<0.001	2.4 ($\pm$ 1.8)	2.5 ($\pm$ 1.6)	0.560
Hemoglobin (g/dl)	14 ($\pm$ 1)	14 ($\pm$ 1)	<0.001	14 ($\pm$ 1)	14 ($\pm$ 1)	0.809
White blood count ($10^3/\mu$ l)	6.2 ($\pm$ 2.0)	6.8 ($\pm$ 2.7)	<0.001	7 ($\pm$ 3)	7 ($\pm$ 2)	0.547
Platelets ($10^3/\mu$ l)	252 ($\pm$ 75)	243 ($\pm$ 75)	0.001	247 ($\pm$ 73)	244 ($\pm$ 75)	0.410
Electrocardiographic findings						
Left ventricular hypertrophy	192 (4%)	44 (5%)	0.217	38 (5%)	33 (5%)	0.625
Atrial fibrillation	91 (2%)	24 (3%)	0.130	17 (2%)	16 (2%)	1.000
Bundle branch block	357 (8%)	103 (12%)	<0.001	84 (12%)	83 (12%)	1.000
LV systolic dysfunction	318 (7%)	93 (11%)	<0.001	62 (9%)	71 (10%)	0.478

Table 2

Association of baseline diabetes mellitus and incident heart failure among community-dwelling older adults without heart failure, before and after propensity matching

	% (events/total)		Diabetes mellitus	Absolute risk difference [*] (%)	Hazard ratio [†] (95% confidence interval)	P value
	No diabetes mellitus	Diabetes mellitus				
Unadjusted	19% (862/4602)	32% (272/862)		+13%	2.22 (1.94–2.55)	<0.001
Multivariable adjusted	---	---		---	1.52 (1.30–1.78)	<0.001
Propensity matched	26% (183/717)	31% (220/717)		+5%	1.45 (1.14–1.86)	0.003

^{*} Absolute risk differences were calculated by subtracting the percentage of events in the no diabetes group from that of the diabetes group

[†] Hazard ratios comparing diabetes to no diabetes

Table 3

Association of baseline diabetes mellitus and all-cause and cause-specific mortalities among community-dwelling older adults without heart failure, before and after propensity matching

	% (events/total)		Absolute risk difference [*] (%)	Hazard ratio [†] (95% confidence interval)	P value
	No diabetes mellitus	Diabetes mellitus			
All-cause mortality					
Unadjusted	41% (1895/4602)	59% (509/862)	+18%	1.82 (1.65–2.01)	<0.001
Multivariable adjusted	---	---	---	1.44 (1.29–1.62)	<0.001
Propensity matched	47% (334/717)	57% (408/717)	+10%	1.35 (1.13–1.61)	0.001
Cardiovascular mortality					
Unadjusted	16% (724/4602)	29% (248/862)	+13%	2.31 (2.00–2.67)	<0.001
Multivariable adjusted	---	---	---	1.65 (1.40–1.95)	<0.001
Propensity matched	20% (142/717)	27% (192/717)	+7%	1.53 (1.23–1.91)	<0.001
Non-cardiovascular mortality					
Unadjusted	25% (1165/4602)	30% (260/862)	+5%	1.52 (1.33–1.74)	<0.001
Multivariable adjusted	---	---	---	1.32 (1.13–1.53)	<0.001
Propensity matched	27% (190/717)	30% (215/717)	+3%	1.30 (1.07–1.58)	0.008

^{*} Absolute risk differences were calculated by subtracting the percentage of events in the no diabetes group from that of the diabetes group

[†] Hazard ratios comparing diabetes to no diabetes

Association of baseline diabetes mellitus and other outcomes among community-dwelling older adults without HF, before and after propensity matching

Table 4

	% (events/total)		Absolute risk difference [*] (%)	Hazard ratio [†] (95% confidence interval)	P value
	No diabetes mellitus	Diabetes mellitus			
<u>Incident acute myocardial infarction</u>					
Unadjusted	10% (464/4602)	14% (122/862)	+4%	1.72 (1.41–2.10)	<0.001
Multivariable adjusted	---	---	---	1.29 (1.03–1.62)	0.028
Propensity matched	12% (85/717)	14% (102/717)	+2%	1.37 (0.97–1.93)	0.072
<u>Incident stroke</u>					
Unadjusted	13% (583/4602)	15% (133/862)	+3%	1.51 (1.25–1.82)	<0.001
Multivariable adjusted	---	---	---	1.30 (1.05–1.60)	0.016
Propensity matched	14% (99/717)	15% (107/717)	+1%	1.11 (0.81–1.51)	0.527
<u>Peripheral arterial disease</u>					
Unadjusted	3% (139/4602)	8% (65/862)	+5%	3.01 (2.24–4.04)	<0.001
Multivariable adjusted	---	---	---	2.22 (1.57–3.16)	<0.001
Propensity matched	4% (27/717)	7% (51/717)	+3%	2.50 (1.45–4.32)	0.001

* Absolute risk differences were calculated by subtracting the percentage of events in the no diabetes group from that of the diabetes group

† Hazard ratios comparing diabetes to no diabetes