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Prediabetes is not an independent risk factor for incident heart failure, other cardiovascular events or mortality in older adults: Findings from a population-based cohort study

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Abstract

Background—Whether prediabetes is an independent risk factor for incident heart failure (HF) in non-diabetic older adults remains unclear.

Methods—Of the 4602 Cardiovascular Health Study participants, age ≥ 65 years, without baseline HF and diabetes, 2157 had prediabetes, defined as fasting plasma glucose (FPG) 100–125 mg/dL. Propensity scores for prediabetes, estimated for each of the 4602 participants, were used to assemble a cohort of 1421 pairs of individuals with and without prediabetes, balanced on 44 baseline characteristics.

Results—Participants had a mean age of 73 years, 57% were women, and 13% African American. Incident HF occurred in 18% and 20% of matched participants with and without prediabetes, respectively (hazard ratio {HR} associated with prediabetes, 0.90; 95% confidence interval {CI}, 0.76–1.07; p = 0.239). Unadjusted and multivariable-adjusted HRs (95% CIs) for incident HF associated with prediabetes among 4602 pre-match participants were 1.22 (95% CI, 1.07–1.40; p = 0.003) and 0.98 (95% CI, 0.85–1.14; p = 0.826), respectively. Among matched individuals, prediabetes had no independent association with incident acute myocardial infarction (HR, 1.02; 95% CI, 0.81–1.28; p = 0.875), angina pectoris (HR, 0.93; 95% CI, 0.77–1.12; p = 0.451), stroke (HR, 0.86; 95% CI, 0.70–1.06; p = 0.151) or all-cause mortality (HR, 0.99; 95% CI, 0.88–1.11; p = 0.840).

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Conclusions—We found no evidence that prediabetes is an independent risk factor for incident HF, other cardiovascular events or mortality in community-dwelling older adults. These findings question the wisdom of routine screening for prediabetes in older adults and targeted interventions to prevent adverse outcomes in older adults with prediabetes.

Keywords

Prediabetes; Diabetes; Heart failure; Older adults; Propensity-matched study

1. Introduction

Prediabetes is associated with increased risk of type II diabetes [1], which in turn is associated with poor cardiovascular outcomes [2,3]. Prediabetes has also been observed to be associated with higher risk of cardiovascular events in younger adults [4]. However, it is unknown whether prediabetes would also be associated with poor outcomes in older adults who might be exposed to multiple other competing risk factors. Further, whether the association of prediabetes with cardiovascular events is truly independent has not been examined in well-balanced propensity score-matched populations [5,6]. Importantly, if prediabetes indeed had an independent association with incident cardiovascular events, whether that would translate into higher mortality in older adults with prediabetes has not been previously examined. This is important as the prevalence of prediabetes increases with age [7]. Therefore, we examined the independent associations of prediabetes with incident heart failure (HF) and otherb cardiovascular events, and all-cause and cause-specific mortalities in propensity-matched cohorts of community-dwelling older adults in the Cardiovascular Health Study (CHS).

2. Methods

2.1. Study design and participants

The CHS is a National Heart, Lung, and Blood Institute (NHLBI)-funded longitudinal study of community-dwelling older adults to identify the presence and severity of traditional as well as new risk factors for cardiovascular disease among older adults [8]. Participants aged ≥ 65 years were recruited in two phases from four communities: Forsyth County, North Carolina, Sacramento County, California, Washington County, Maryland, and Pittsburgh, Pennsylvania. An original cohort (n = 5201) was recruited between 1989 and 1990, and a second cohort (n = 687) of African-Americans was recruited between 1992 and 1993 [9].

For the current analysis, we used a de-identified public-use copy of the CHS data obtained from the NHLBI, which is similar to the main CHS data, except that 93 participants did not consent to be included in that data. From the 5795 participants in the public-use copy of the data, we excluded 79 participants with missing baseline fasting plasma glucose (FPG) data, 930 participants with baseline diabetes, defined by the 2008 American Diabetes Association (ADA) criterion of FPG level ≥ 126 mg/dL [10] or treatment with insulin or hypoglycemic drugs, and 184 participants with centrally-adjudicated baseline prevalent HF [11], resulting in a final sample size of 4602 participants for the current analysis (Fig. 1).

2.2. Prediabetes and other baseline measurements

Of the 4602 participants without baseline diabetes, 2157 (47%) had prediabetes based on the ADA criterion of FPG 100–125 mg/dL [10], leaving 2445 (53%) without baseline prediabetes or diabetes. Data on demographic, clinical and laboratory variables were collected at baseline and have been previously described in detail [8,9]. Missing values were imputed using values predicted by age, sex and race.

Because only the original CHS cohort had data on oral glucose tolerance test (OGTT), we assembled a second cohort to estimate the association of prediabetes based on impaired OGTT. Of the 4602 CHS participants without baseline diabetes based on baseline FPG, 4151 (90%) belonged to the CHS original cohort. Of these, 425 (10%) had diabetes based on OGTT. After excluding these 425 participants with diabetes, the cohort for OGTT analysis included 3726 participants, of whom 2431 (65%) had no prediabetes or diabetes (normal OGTT), and 1295 (35%) had prediabetes (impaired OGTT).

2.3. Outcome measures

The primary outcome of interest for the current analysis was incident HF during 13 years of total follow-up. The CHS Events Committee centrally adjudicated incident HF and other outcomes and the process of adjudication has been previously described [9,12,13]. Briefly, self-reports of physician-diagnosed HF were obtained during semi-annual visits, which were later on verified through the review of medical records for symptoms, signs and clinical findings, use of medications commonly used for HF and follow-up surveillance assessments. Secondary outcomes were all-cause mortality, cause-specific mortality and other incident cardiovascular events such as acute myocardial infarction, angina pectoris, stroke, and peripheral artery disease. To account for the competing risk of death on incident HF, we also estimated the association of prediabetes with the composite endpoint of incident HF or all-cause mortality. All outcomes were centrally adjudicated by the CHS events committee and have been previously described [11,13].

2.4. Assembly of a balanced study cohort

Due to significant imbalances in pre-match baseline characteristics between participants with and without prediabetes (Table 1 and Fig. 2), we used propensity score matching to assemble a cohort in which those with and without prediabetes would be well-balanced on all measured baseline covariates [5,6,14,15]. The propensity score for prediabetes is the conditional probability of having prediabetes given a set of baseline covariates. We estimated a propensity score for prediabetes (FPG 100–125 mg/dL) for each of the 4602 participants using a non-parsimonious multivariable logistic regression model based on the 44 baseline characteristics shown in Fig. 2 [16–20]. Using a greedy matching protocol described elsewhere, we assembled a cohort of 1421 pairs of participants with and without prediabetes who had similar propensity scores [21–23]. Absolute standardized differences were estimated to quantify bias in the means of covariates across the groups and are displayed in a Love plot [5,21–23]. An absolute standardized difference of 0% indicates no residual bias and we regard absolute standardized differences <10% is ignorable.

2.5. Statistical analysis

Descriptive analyses used Pearson's Chi-square, Wilcoxon rank-sum, McNemar's and paired sample t-tests to compare those with and without prediabetes as appropriate. Kaplan Meier analyses and Cox proportional hazard models were used to evaluate the associations of prediabetes with incident HF and other outcomes in the post-match cohorts. To examine interaction with age and insulin resistance, we examined these associations by age tertile and homeostasis model assessment–insulin resistance (HOMA-IR) median. A multivariable Cox regression model, adjusting for all covariates used in the propensity model as displayed in Fig. 2, was used to estimate hazard ratios (HR) associated with prediabetes among pre-match participants. We also examined the incidence of diabetes during follow-up but before incidence of HF, and used logistic regression analysis to compare incident diabetes between those with and without prediabetes. All statistical tests were two-tailed with 95% confidence levels (CI), and SPSS for Windows (Rel. 18, 2009; Chicago: SPSS Inc.) was used for all data analysis.

3. Results

3.1. Baseline characteristics

Matched participants had a mean (±SD) age of 73 (±6) years, 57% were women, and 13% were African Americans. Before matching, compared to the no prediabetes group, subjects with prediabetes were more likely to be male, white, had coronary artery disease, hypertension, chronic kidney disease, and had higher mean body mass index. These and all of the remaining 44 measured baseline characteristics were balanced after matching (Table 1 and Fig. 2). Post-match absolute standardized differences for all measured covariates were <10%, suggesting substantial covariate balance between the two groups (Fig. 2).

3.2. Association of prediabetes with incident heart failure

Incident HF occurred in 18% and 20% of matched participants with and without prediabetes, respectively (HR, 0.90; 95% CI, 0.76–1.07; p = 0.239; Fig. 3 and Table 2). Unadjusted, multivariable-adjusted and propensity-adjusted associations of prediabetes with incident HF among pre-match participants are displayed in Table 2. Pre-diabetes-associated HRs (95% CIs) for incident HF for matched participants age < 70, 70–75, ≥76 years were 0.95 (0.64–1.41; p = 0.798), 0.92 (0.69–1.24; p = 0.593), and 0.85 (0.67–1.09; p = 0.199), respectively. Prediabetes-associated HRs (95% CIs) for incident HF for matched participants at or below and above median HOMA-IR were 0.90 (0.70–1.14; p = 0.381) and 0.92 (0.72–1.17; p = 0.501), respectively. Among matched individuals, prediabetes had no association with the composite endpoint of all-cause mortality or incident HF (HR, 0.98; 95% CI, 0.88–1.09; p = 0.661). This association did not vary by age tertile or HOMA-IR median.

When prediabetes was defined as impaired 2-hour OGTT, unadjusted and multivariable-adjusted HRs for incident HF associated with prediabetes were 1.33 (95% CI, 1.14–1.54; p < 0.001) and 1.06 (95% CI, 0.90–1.25; p = 0.474), respectively.

3.3. Association of prediabetes with other incident cardiovascular events

Prediabetes had a significant unadjusted association with incident acute myocardial infarction (unadjusted HR, 1.24; 95% CI, 1.03–1.48; p = 0.022) and angina pectoris (unadjusted HR, 1.23; 95% CI, 1.06–1.43; p = 0.005) but not with stroke (unadjusted HR, 0.99; 95% CI, 0.84–1.17; p = 0.924; Table 3). However, these associations became non-significant after multivariable adjustment for baseline confounders, adjustment for propensity scores, and in the propensity-matched cohort (Table 3).

3.4. Association of prediabetes with mortality

All-cause mortality occurred in 43% and 39% of pre-match participants with and without prediabetes, respectively (unadjusted HR, 1.14; 95% CI, 1.04–1.25; p = 0.005; Table 4) and in 42% of matched participants both with and without prediabetes (matched HR, 0.99; 95% CI, 0.88–1.11; p = 0.840; Fig. 4 and Table 4). This association did not vary by age tertile or HOMA-IR median. The associations of prediabetes with cardiovascular and non-cardiovascular mortalities are displayed in Table 4.

3.5. Association of prediabetes with incident diabetes

Of the 4602 participants without diabetes and prevalent HF at baseline, 3889 had data on diabetes status during follow-up. Overall, 183 (4%) had developed incident diabetes before incident HF, which occurred in 148 (8%) and 35 (2%) of those with and without pre-diabetes, respectively (unadjusted odds ratio {OR}, 5.18; 95% CI, 3.56–7.53; p < 0.001). Incident diabetes before incident HF occurred in 7% (85/1195) and 2% (24/1202) of

matched participants with and without prediabetes, respectively (OR, 3.78; 95% CI, 2.37–5.96; $p < 0.001$).

3.6. Association of incident diabetes with outcomes

Incident HF occurred in 20% (36/183) and 21% (772/3706) of participants with and without incident diabetes, respectively ($p = 0.706$). All-cause mortality occurred in 32% (58/183) of participants with incident diabetes and 39% (1451/3706) of those who did not develop new-onset diabetes (unadjusted OR associated with incident diabetes, 0.72; 95% CI, 0.53–0.99; $p = 0.044$). Those with incident diabetes were younger than those without diabetes (mean age 71.5 versus 73.3 years for those with and without incident diabetes respectively; $p < 0.001$) and adjustment for age alone made this association non-significant (age-adjusted HR, 0.94; 95% CI, 0.67–1.31; $p = 0.695$). Additional adjustment in a multivariable model did not alter this association (adjusted HR, 0.93; 95% CI, 0.64–1.35; $p = 0.691$).

4. Discussion

4.1. Brief summary of the key findings

In community-dwelling older adults without diabetes, prediabetes was associated with higher unadjusted risk of incident HF, other cardiovascular events and mortality. However, there was no evidence that any of these associations were independent of other confounding risk factors. Although prediabetes increased the risk of incident diabetes, the absolute rate of incident diabetes was low and incident diabetes by itself was also not an independent predictor of poor cardiovascular outcomes, likely due to deaths from other competing risk factors before the development of diabetes-related complications in older adults with incident diabetes. Prediabetes is often targeted for intervention efforts for the prevention of diabetes and subsequent adverse cardiovascular events. Findings from the current study suggest that such interventions may not improve cardiovascular outcomes in older adults.

4.2. Potential explanations for the key findings

Observed unadjusted associations of prediabetes with incident HF and other cardiovascular events are likely attributable to confounding as these associations disappeared after these confounders were accounted for. An increased cardiovascular risk in those with prediabetes would be expected to be mediated through an increased risk of incident diabetes. However, the low incidence of diabetes and short follow-up after incident diabetes may have precluded the manifestation of adverse cardiovascular effects associated with diabetes. This is supported by our observation that incident diabetes in general had no significant association with HF and all-cause mortality. It is also possible that new-onset diabetes in older adults is pathophysio-logically different from that in younger patients [24]. The recent decrease of the FPG cutoff from 110 mg/dL to 100 mg/dL by the ADA to define impaired fasting glucose (IFG) may also help explain the observed non-significant associations between prediabetes and cardiovascular outcomes [25]. Another potential explanation is that older adults with incident diabetes might die from other competing risk factors before development of diabetes-related complications [26].

4.3. Comparison with relevant published findings

A previous study of the original CHS cohort demonstrated that the FPG ≥ 115 mg/dL (versus <115 mg/dL) was associated with cardiovascular events [27]. In that study, FPG ≥ 115 group also included those with untreated diabetes and incident HF was not an end point. In a study of younger (mean age, ∼ 60 years) veterans without a history of diabetes, serum glucose was associated with incident HF [28]. A meta-regression analysis of 20 prospective studies demonstrated that the risk of cardiovascular events progressively increased with increasing serum glucose levels, even among those without diabetes [29]. A recent

systematic review also reported an association of pre-diabetes with higher risk of incident cardiovascular disease [4]. Although that study did not report age, most of the participants were young and middle aged. For example, of the eighteen studies that used the same ADA criterion as in the current study, the two studies with the highest weights were based on men 40 to 59 years of age and men and women 30 to 89 years of age (mean, about 53 years), respectively [30,31]. In contrast to the aforementioned studies, our study is distinguished by the use of FPG, exclusion of patients with prevalent HF at baseline, central adjudication of incident HF, long-term follow up, the use of propensity scores to assemble a balanced cohort, and sensitivity analysis using various definitions of prediabetes.

4.4. Potential clinical and/or public health implications

Findings from the National Health and Nutrition Examination Survey (2005–2006) demonstrated that nearly 30% of Americans ≥ 20 years have prediabetes, which increases to about 50% for those ≥ 75 years [7]. The ADA recommends diabetes prevention for selected high-risk individuals with prediabetes [32]. Because such interventions have been shown to reduce the incidence of diabetes, it is tempting to conclude that they would also reduce cardiovascular events. However, a recent meta-analysis of randomized clinical trials of prediabetes interventions (n = 23,152) has demonstrated that while there was a significant reduction in incident diabetes, there was no reduction in all-cause mortality or cardiovascular events [33]. Although that study included both younger and older patients, findings from our study suggest given the lack of an independent association between prediabetes and poor outcomes in older adults, such interventions are unlikely to improve outcomes in older adults with prediabetes [26].

4.5. Limitations

Our study has several limitations. Participants without pre-diabetes may have developed prediabetes during follow-up, thus causing regression dilution and underestimation of the true association [34]. However, the higher incidence of diabetes among those with prediabetes may have cancelled that out. In addition, our sample size might be relatively small. It is possible that some individuals with elevated HbA1c but normal FPG were misclassified as prediabetes [35]. However, CHS only had a single baseline FPG level and did not collect data on HbA1c. In one study, HbA1c of 6.5% or higher identified fewer individuals with diabetes than those identified by the ADA criterion of criterion of FPG level ≥ 126 mg/dL [36]. We also do not have follow-up data on left ventricular ejection fraction. Naturally, our findings based on older adults may not be generalized to younger adults. However, despite suggestions of higher risk of cardiovascular events in younger and middle-age adults with prediabetes [4], interventions do not seem to reduce all-cause mortality or cardiovascular events in these patients [33].

4.6. Conclusions

Among community-dwelling older adults, we found no evidence of an independent association of prediabetes with higher risk of incident HF, other cardiovascular events or mortality. This is in contrast to the reported association of prediabetes with higher risk of these outcomes in younger and middle-aged adults, and is likely explained in part by the fact that older adults with new-onset diabetes might die from other competing risk factors for mortality, before developing diabetes-related cardiovascular or other complications. Findings from this study should not be generalized to younger and middle-aged adults with prediabetes. Although currently there is no effective intervention to reduce all-cause mortality or cardiovascular events in those with prediabetes [33], definite answers await future large scale prospective randomized clinical trials. However, findings of the current study suggest that there is no evidence that targeted interventions may reduce risk of adverse

cardiovascular events and death in community-dwelling older adults with prediabetes and thus, older adults should not be routinely screened for prediabetes.

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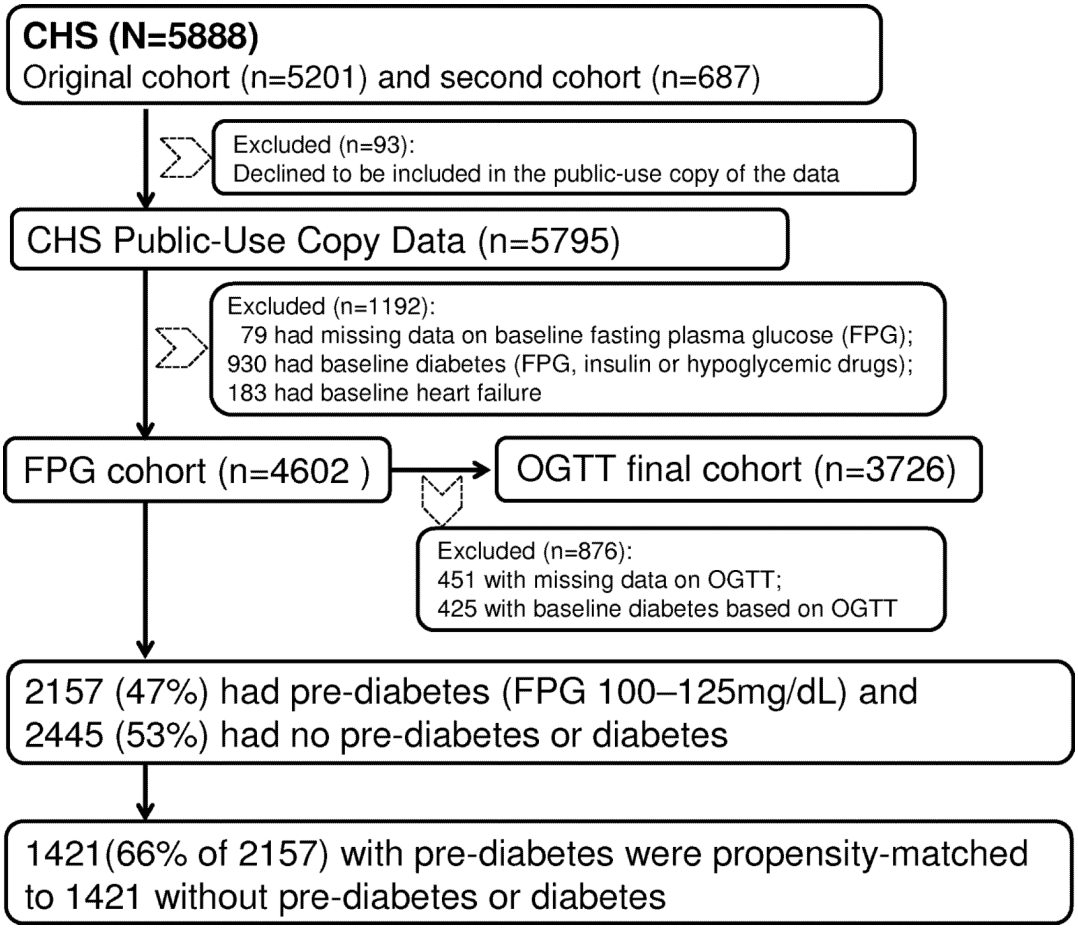


Fig. 1.
Flow chart displaying assembly of the study cohort.

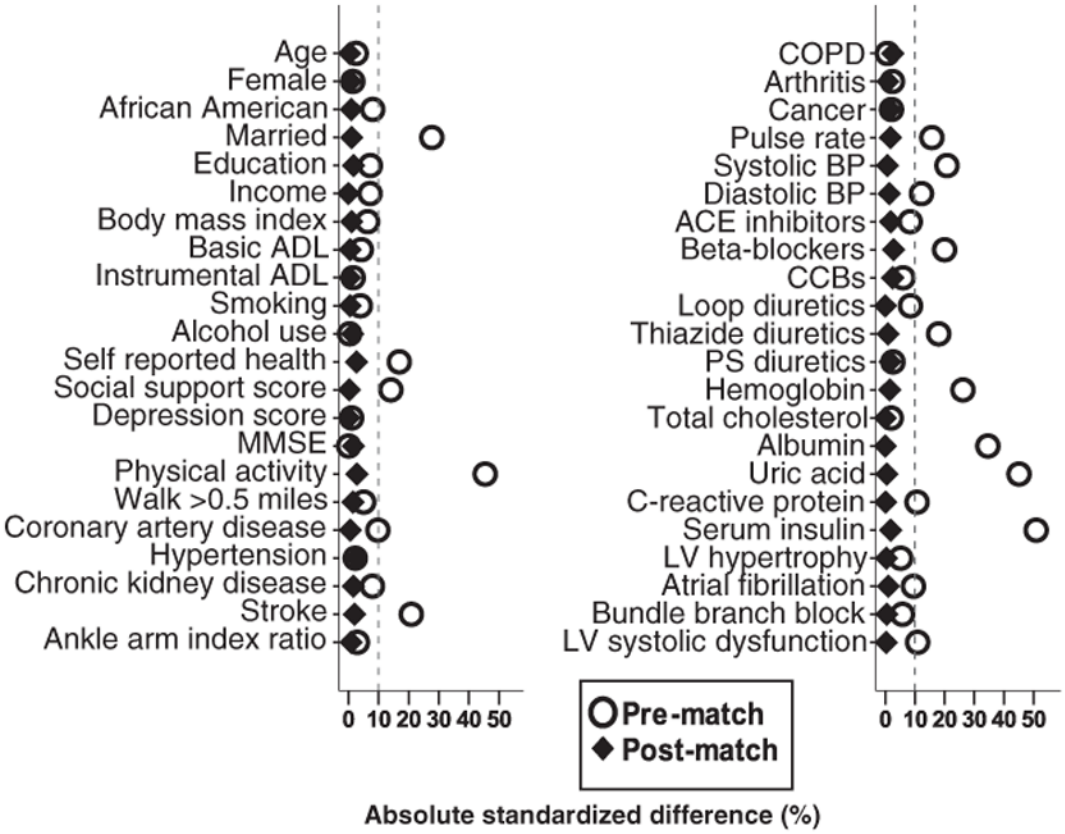


Fig. 2.

Love plot comparing absolute standardized differences of 44 baseline characteristics between diabetes-free older adults with and without prediabetes, before and after propensity score matching (ACE = angiotensin-converting enzyme; ADL = activities of daily living; BP = blood pressure; CCB = calcium channel blockers; COPD = chronic obstructive pulmonary disease; LV = left ventricular; MMSE = Mini-Mental State Examination; PS = potassium sparing).

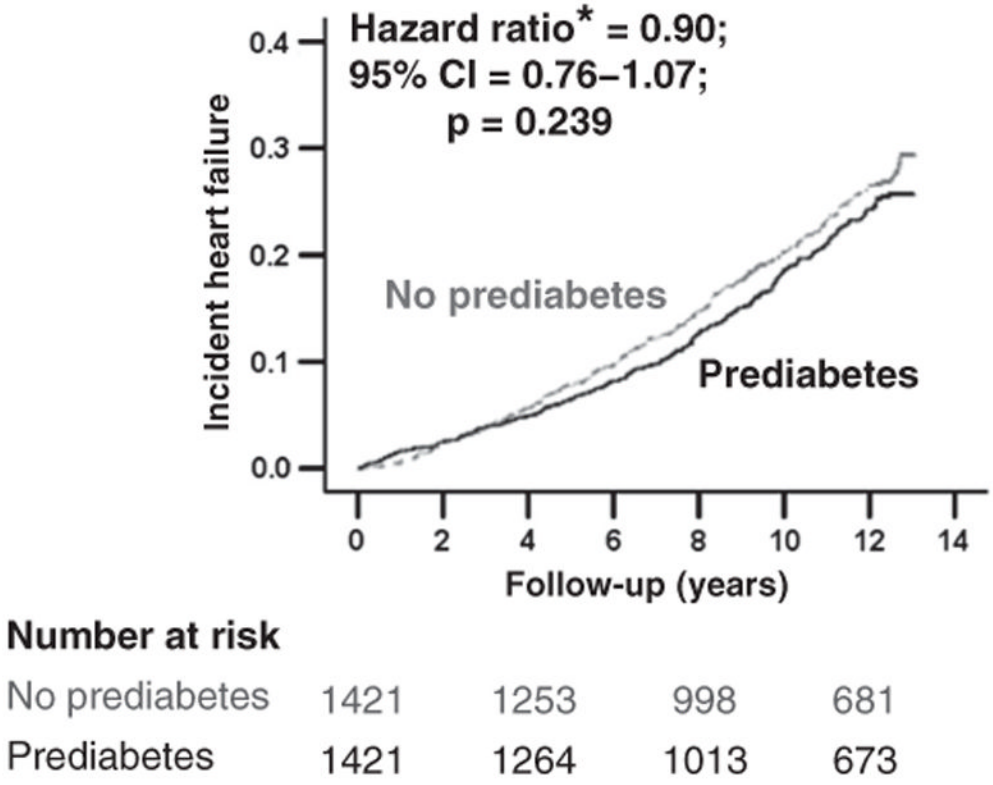
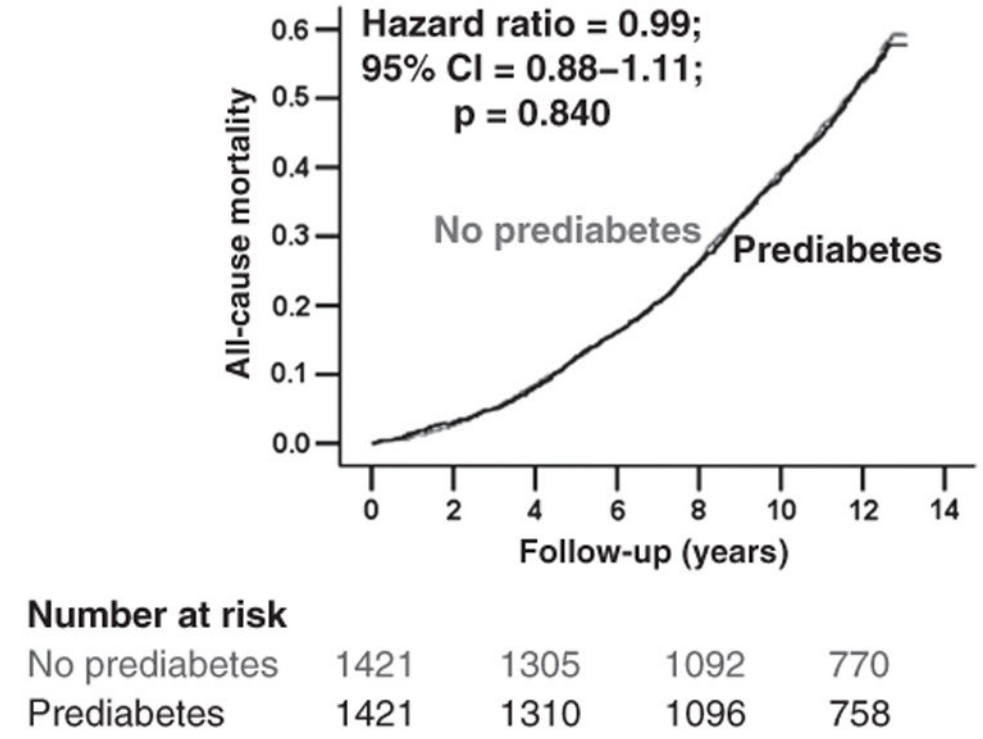


Fig. 3.

Kaplan–Meier plot for incident heart failure by prediabetes among propensity-matched older adults without diabetes (*Hazard ratio when individuals with prediabetes were compared to those without prediabetes; CI=confidence interval).



Number at risk

No prediabetes	1421	1305	1092	770
Prediabetes	1421	1310	1096	758

Fig. 4.

Kaplan–Meier plot for all-cause mortality by prediabetes among propensity-matched older adults without diabetes (*Hazard ratio when individuals with prediabetes were compared to those without prediabetes; CI=confidence interval).

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Table 1

Baseline characteristics by prediabetes.

N (%) or mean (± SD)	Before matching			After matching		
	Prediabetes		p value	Prediabetes		p value
	No (n = 2445)	Yes (n = 2157)		No (n = 1421)	Yes (n = 1421)	
Age, years	73 (±6)	73 (±6)	0.302	73 (±6)	73 (±6)	0.806
Female	1559 (64%)	1155 (54%)	<0.001	807 (57%)	821 (58%)	0.618
African American	355 (15%)	255 (12%)	0.007	184 (13%)	192 (14%)	0.697
Married	1635 (67%)	1466 (68%)	0.430	953 (67%)	970 (68%)	0.516
College or higher education	1143 (47%)	903 (42%)	0.001	618 (44%)	614 (43%)	0.909
Income ≥ $25 thousand	962 (39%)	795 (37%)	0.083	531 (37%)	541 (38%)	0.727
Fair and poor general health	502 (21%)	446 (21%)	0.903	303 (21%)	295 (21%)	0.746
Activities of daily living	0.1 (±0.4)	0.1 (±0.5)	0.986	0.1 (±0.4)	0.1 (±0.4)	0.759
Instrumental activities of daily living	0.3 (±0.7)	0.3 (±0.7)	0.701	0.3 (±0.7)	0.3 (±0.7)	0.979
Walking 0.5 mile without difficulty	2092 (86%)	1789 (83%)	0.015	1195 (84%)	1195 (84%)	1.000
Smoking, pack years	15 (±24)	19 (±28)	<0.001	17 (±26)	17 (±25)	0.926
Alcohol intake, units/week	2 (±5)	3 (±8)	<0.001	3 (±6)	3 (±7)	0.447
Energy expended, kcal/week	1757 (±1833)	1639 (±1823)	0.030	1736 (±1845)	1716 (±1862)	0.770
Body mass index, kg/m^2	25 (±4)	27 (±4)	<0.001	26 (±4)	26 (±4)	0.401
Medical history						
Coronary artery disease	364 (15%)	379 (18%)	0.014	225 (16%)	234 (17%)	0.685
Hypertension	1202 (49%)	1354 (63%)	<0.001	800 (56%)	808 (57%)	0.781
Chronic kidney disease	468 (19%)	484 (22%)	0.006	295 (21%)	301 (21%)	0.818
Stroke	85 (4%)	69 (3%)	0.601	50 (4%)	48 (3%)	0.918
Peripheral arterial disease[a]	262 (11%)	249 (12%)	0.372	163 (12%)	165 (12%)	0.952
Arthritis	1251 (51%)	1078 (50%)	0.421	713 (50%)	707 (50%)	0.851
Cancer	364 (15%)	305 (14%)	0.473	188 (13%)	196 (14%)	0.708
Medications						
Angiotensin converting enzyme inhibitors	113 (5%)	141 (7%)	0.005	83 (6%)	77 (5%)	0.677
Beta-blockers	219 (9%)	334 (16%)	<0.001	169 (12%)	182 (13%)	0.485
Calcium channel blockers	258 (11%)	269 (13%)	0.041	149 (11%)	160 (11%)	0.548

N (%) or mean (± SD)	Before matching			After matching		
	Prediabetes		p value	Prediabetes		p value
	No (n = 2445)	Yes (n = 2157)		No (n = 1421)	Yes (n = 1421)	
Loop diuretics	78 (3%)	105 (5%)	0.004	55 (4%)	55 (4%)	1.000
Potassium sparing diuretics	16 (1%)	19 (1%)	0.378	12 (1%)	10 (1%)	0.832
Thiazide diuretics	196 (8%)	293 (14%)	<0.001	144 (10%)	148 (10%)	0.847
Aspirin	77 (3%)	63 (3%)	0.652	40 (3%)	41 (3%)	1.000
Statins	54 (2%)	40 (2%)	0.397	32 (2%)	28 (2%)	0.699
Pulse, beats/min	66 (±10)	68 (±11)	<0.001	68 (±10)	67 (±11)	0.639
Systolic blood pressure, mm Hg	134 (±21)	138 (±21)	<0.001	136 (±21)	137 (±22)	0.841
Diastolic blood pressure, mm Hg	70 (±11)	72 (±11)	<0.001	71 (±11)	71 (±11)	0.721
Electrocardiographic findings						
Left ventricular hypertrophy	90 (4%)	102 (5%)	0.076	55 (4%)	56 (4%)	1.000
Atrial fibrillation	33 (1%)	58 (3%)	0.001	28 (2%)	26 (2%)	0.892
Bundle branch block	172 (7%)	185 (9%)	0.051	115 (8%)	117 (8%)	0.946
Echocardiographic finding						
Left ventricular ejection fraction < 55%	137 (6%)	181 (8%)	<0.001	101 (7%)	100 (7%)	1.000
Laboratory values						
Total cholesterol, mg/dL	212 (±38)	213 (±39)	0.497	213 (±38)	213 (±38)	0.997
Albumin, g/dL	3.9 (±0.3)	4.0 (±0.3)	<0.001	4.0 (±0.3)	4.0 (±0.3)	1.000
Uric acid, mg/dL	5.3 (±1.4)	6.0 (±1.5)	<0.001	5.7 (±1.4)	5.7 (±1.4)	0.870
C-reactive protein, mg/dL	3.9 (±6.5)	4.6 (±7.4)	<0.001	4.3 (±7.1)	4.3 (±7.0)	0.973
Serum insulin, μIU/mL	12 (±5)	16 (±10)	<0.001	13 (±6)	14 (±6)	0.520
Hemoglobin, g/dL	13.8 (±1.3)	14.2 (±1.3)	<0.001	14 (±1)	14 (±1)	0.678

[a]Defined as ankle brachial index < 0.9.

Table 2

Association of prediabetes with incident heart failure.

Outcomes	Events, % (n/N)		Absolute risk difference (%)[a]	Hazard ratio[b] (95% CI)	p value
	No prediabetes	prediabetes			
Pre-match cohort					
Unadjusted	17% (424/2445)	20% (438/2157)	+ 3%	1.22 (1.07–1.40)	0.003
Multivariable-adjusted	–	–	–	0.98 (0.85–1.14)	0.826
Propensity-adjusted	–	–	–	0.94 (0.81–1.09)	0.397
Matched cohort	20% (282/1421)	18% (256/1421)	– 2%	0.90 (0.76–1.07)	0.239

[a] Absolute risk differences were calculated by subtracting the percentage of events in the no prediabetes group from that of the prediabetes group before rounding.

[b] Hazard ratios comparing prediabetes to no prediabetes group.

Table 3

Association of prediabetes with other incident cardiovascular events.

Outcomes	Events, % (n/N)		Absolute risk difference (%)[a]	Hazard ratio[b] (95% CI)	p value
	No prediabetes	prediabetes			
Incident acute myocardial infarction					
Unadjusted	10% (226/2281)	12% (238/1989)	+ 2%	1.24 (1.03–1.48)	0.022
Multivariable-adjusted	–	–	–	1.01 (0.83–1.23)	0.927
Propensity-adjusted	–	–	–	1.01 (0.82–1.23)	0.939
Propensity matched	11% (143/1313)	11% (148/1323)	0%	1.02 (0.81–1.28)	0.875
Incident angina pectoris					
Unadjusted	17% (355/2145)	20% (363/1840)	+ 3%	1.23 (1.06–1.43)	0.005
Multivariable-adjusted	–	–	–	0.99 (0.84–1.16)	0.853
Propensity-adjusted	–	–	–	1.00 (0.85–1.17)	0.987
Propensity matched	19% (230/1241)	17% (212/1219)	– 2%	0.93 (0.77–1.12)	0.451
Incident stroke					
Unadjusted	13% (314/2360)	13% (269/2088)	0%	0.99 (0.84–1.17)	0.924
Multivariable-adjusted	–	–	–	0.86 (0.72–1.03)	0.092
Propensity-adjusted	–	–	–	0.85 (0.71–1.02)	0.074
Propensity matched	14% (187/1371)	12% (162/1373)	– 2%	0.86 (0.70–1.06)	0.151

[a] Absolute risk differences were calculated by subtracting the percentage of events in the no prediabetes group from that of the prediabetes group before rounding.

[b] Hazard ratios comparing prediabetes to no prediabetes group.

Table 4

Association of prediabetes with mortality.

Outcomes	Events, % (n/N)		Absolute risk difference (%)[a]	Hazard ratio[b] (95% CI)	p value
	No prediabetes	Prediabetes			
All-cause mortality					
Unadjusted	39% (959/2445)	43% (936/2157)	+ 4%	1.14 (1.04–1.25)	0.005
Multivariable-adjusted	–	–	–	1.03 (0.93–1.14)	0.572
Propensity-adjusted	–	–	–	1.00 (0.91–1.11)	0.955
Propensity matched	42% (599/1421)	42% (591/1421)	0%	0.99 (0.88–1.11)	0.840
Cardiovascular mortality					
Unadjusted	15% (366/2445)	17% (358/2157)	+ 2%	1.14 (0.99–1.32)	0.077
Multivariable-adjusted	–	–	–	0.97 (0.83–1.14)	0.720
Propensity-adjusted	–	–	–	0.92 (0.79–1.08)	0.322
Propensity matched	18% (251/1421)	15% (215/1421)	-3%	0.86 (0.72–1.03)	0.099
Non-cardiovascular mortality					
Unadjusted	24% (590/2445)	27% (575/2157)	+ 3%	1.14 (1.01–1.27)	0.030
Multivariable-adjusted	–	–	–	1.07 (0.94–1.21)	0.292
Propensity-adjusted	–	–	–	1.06 (0.93–1.20)	0.405
Propensity matched	24% (347/1421)	26% (375/1421)	+ 2%	1.08 (0.94–1.25)	0.286

[a] Absolute risk differences were calculated by subtracting the percentage of events in the no prediabetes group from that of the prediabetes group before rounding.

[b] Hazard ratios comparing prediabetes to no prediabetes group.