The Effect of Adherence to Screening Guidelines on the Risk of Alzheimer’s Disease in Elderly Individuals Newly Diagnosed With Type 2 Diabetes Mellitus

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Abstract

Objective: The aim of this study was to examine the possibility that type 2 diabetes and Alzheimer’s disease may share common behavioral protective factors such as adherence to type 2 diabetes treatment guidelines given that these two diseases have both epidemiological and metabolic similarities. Method: The method used in this study is a retrospective cohort study of 3,797 U.S. Medicare fee-for-service beneficiaries aged 66+ newly diagnosed with type 2 diabetes and without a prior record of Alzheimer’s disease based on the Health and Retirement Study. Results: Results of a left-truncated Cox model showed that adherence reduces the risk of Alzheimer’s disease by 20% to 24%. Other significant effects were college education (hazard ratio [HR]: 0.65; p value: .023), stroke (HR: 1.40; p value: .013), and 4+ limitations in physical functioning (HR: 1.33; p value: .008). Discussion: Risk of Alzheimer’s disease can be reduced by behavioral factors. Possible mechanisms may include earlier start of interventions to reduce blood glucose levels and improve insulin sensitivity.

Keywords
dementia, diabetes, health behaviors, Medicare

Manuscript received: July 25, 2018; final revision received: October 2, 2018; accepted: October 15, 2018

Introduction

Alzheimer’s disease (AD) is a slowly progressing neurodegenerative disorder that results in progressive and irreversible decline in cognitive and functional ability eventually leading to death (Alzheimer’s Association, 2016). At its advanced stages, affected individuals are bed-bound, require constant care and supervision, and experience increased vulnerability to other diseases (Alzheimer’s Association, 2016; Reitz, Brayne, & Mayeux, 2011). The strongest single contributor to AD is age; however, as AD is not part of normal aging (Alzheimer’s Association, 2016), this is, to an extent, a reflection of the fact that the mechanisms responsible for AD start far in advance of identifiable clinical symptoms (Alzheimer’s Association, 2016). Recent research suggests that the age-adjusted incidence rate of AD in the United States was at least constant and may have even decreased over the last quarter-century (Akushevich, Kravchenko, Ukraintseva, Arbeev, & Yashin, 2013; Dodge, Zhu, Lee, Chang, & Ganguli, 2013; L. E. Hebert et al., 2010; Langa et al., 2008; Manton, Gu, & Ukraintseva, 2005; Satizabal et al., 2016). As U.S. lifespan as well as the prevalence of many chronic conditions associated with AD risk such as diabetes, hypertension, and obesity have been increasing, this outcome can be viewed as a positive tendency. One mechanism behind this result could be that the aggressive public health approach aimed at managing the risk for other chronic diseases also affects the risk for AD development at what would otherwise be its asymptomatic stage.

Type 2 diabetes mellitus (T2D) is a serious chronic condition highly prevalent in the United States (Centers for Disease Control and Prevention, 2014). T2D is associated with increased risk of death as well as a range of cerebrovascular, cardiovascular, renal, ocular, lower extremity, and cognitive complications (Akushevich, 2013; Akushevich et al., 2013; Yashkin, Picone, & Sloan, 2015) including AD (Gudala, Bansal, Schifano, 2018).
The use of well-known modifiable health behaviors known to reduce the risk of T2D–related adverse health outcomes to reduce the incidence of AD in the United States.

**Method**

Data drawn from the HRS linked to Medicare Administrative claims (1991-2012) were used for this study. The HRS is an ongoing national, longitudinal survey fielded every other year starting in 1992. Originally, the HRS was designed to be nationally representative of the U.S. community residents aged 50+. In 1998, the Aging Dynamics of the Oldest-Old (AHEAD), a biannual survey representative of individuals age 70+ starting in 1993, was merged with the HRS increasing the total number of persons available for analysis to more than 37,000 individuals. The HRS/AHEAD collects data on a battery of demographic and socioeconomic factors, income, employment, health insurance, physical and cognitive functioning, as well as medical care–related behaviors. Furthermore, Medicare Administrative Claims data are available for more than 22,000 of its participants.

Medicare is a social health insurance program that pays for the health care of the overwhelming majority of the U.S. elderly population. Although there are other ways to qualify, most do so by age—becoming Medicare eligible at 65 years old. Medicare claims data include information on the diagnoses made (International Classification of Disease 9th Edition [ICD-9]) and procedures performed (Current Procedural Terminology and Healthcare Common Procedure Coding System [CPT-4/HCPCS]) in all episodes of care paid for by the Medicare system in either a professional (Part B) or institutional (Part A) setting.

Using Medicare claims, we identified 3,797 individuals newly diagnosed with T2D (Table 1) employing a previously tested algorithm (Akushevich et al., 2016; Yashkin et al., 2015). We excluded individuals below 66 years of age at their baseline date to allow for 1 year of look-back and ensure that the identified cases were, in fact, incident. Individuals enrolled in Medicare Advantage (MA) plans within the 1-year look-back period prior to an identified diagnosis were excluded from the study as most MA plans do not provide claims data for their members making it impossible to differentiate between an incident and prevalent case or identify the presence of comorbid diseases. Individuals were followed until the onset of AD, death, or censoring (last date of available claims or entry into an MA plan).

The ADA (2014) specifies and updates recommended clinical practice guidelines designed to provide a medically proven, consistent approach to the management of T2D. An important aspect of these guidelines is routine screening: annual blood pressure, Hb1AC, urine and cholesterol testing, exams by a physician, yearly eye exams, and consultations with specialist physicians, such as cardiologists, nephrologists,
Yashkin et al.

3

podiatrists, and endocrinologists in the case a T2D complication of the relevant organ system is identified. We combined these recommendations to create an index of adherence to ADA screening guidelines. Information on whether a beneficiary had a blood pressure, urine, HB1AC, and lipid test performed was identified by querying the claims data for the appropriate procedure code (Table 1). Visits to a physician, eye care specialist (optometrist or ophthalmologist), or other T2D specialist were identified from the physician specialty code of the billing physician. Visits to eye care specialists were treated as a separate category as ADA guidelines recommend eye exams on an annual basis, independent of whether the patient experiences symptoms. Factor analysis was conducted to convert the seven measures of health services use into a single adherence index. The first factor was selected as it was the only factor with an eigenvalue above 1.0 (Table 2). Loadings on all variables for the first factor were positive. The adherence factor is a continuous measure with negative values indicating relatively worse adherence and positive values indicating relatively better adherence. Three additional sensitivity analyses using binary cutoff points (adherence ≥ 0.2, ≥0.5, ≥1.0) to indicate adherent/nonadherent individuals were used to test for the stability of the identified effect. Cutoff points were chosen based on the distribution of the continuous adherence factor.

Reduced physical function is both an outcome and a risk factor for T2D/AD. In its role as a risk factor, reduced physical function makes good health behavior such as exercise and regular physician care (outside of institutions) more difficult. As an outcome, AD and many complications of unmanaged or badly managed T2D result in reduced physical function. We used survey data from the HRS to identify whether an individual had difficulty with, or was unable to, (a) walk one block; (b) sit for 2 hr; (c) get up from chair after long period of sitting; (d) climb several flights of stairs without resting; (e) climbing one flight of stairs without resting; (f) stooping, kneeling, and/or crouching; (g) reaching or extending arms above shoulder level; (h) pulling or pushing large objects; (i) lifting or carrying large weights; and (j) picking up a small coin from the table. These data were combined into a 10-point physical functioning index through direct summation and included into our analysis as a binary variable indicating a score of 4 or more on this index (Stenholm et al., 2014). Other covariates included were male gender, White race, being married, college or better education, and the presence of a diagnosis of non-AD dementia, stroke, myocardial infarction, congestive heart failure,

Table 1. List of Study Codes.

| Condition                         | Administrative code |
|-----------------------------------|---------------------|
| Diabetes mellitus                 | ICD-9: 250.xx       |
| Alzheimer’s disease               | ICD-9: 331.0        |
| Dementia                          | ICD-9: 290.0x 290.3x 290.11 290.13 290.20 290.21 290.40-290.43 294.10 294.11 294.20 294.21 331.19 |
| Stroke                            | ICD-9: 431.xx 436.xx 436.01 434.11 434.91 997.02 |
| Myocardial infarction             | ICD-9: 410.xx       |
| Congestive heart failure          | ICD-9: 428.xx 398.91 402.01 402.11 402.91 404.11 404.91 |
| Chronic renal disease             | ICD-9: 585.xx       |
| Blindness                         | ICD-9: 369.xx 360.41 360.42 |
| Lower extremity complication      | ICD-9: 250.7x 730.06 730.07 730.16 730.17 730.26 730.27 785.4x |
| Components of screening adherence |                     |
| Hb1AC test                        | CPT-4: 82985 83036  |
| Lipid test                        | CPT-4: 80061 82465 83715-83719 83721 84478 |
| Urine test                        | CPT-4: 81001 - 81005 82040 82042 82043 82044 84155 |
| Blood pressure test               | CPT-4: 90201 90205 99211-99215 99241-99245 99301-99303 99311-99313 99321-99323 99341-99349 99350 99387 99397 99401-99404 99411 99412 9942x 99331-99333 |
| General practitioner visit        | HCFA: 01 08 11 70 50 97 |
| Optometrist or Ophthalmologist visit | HCFA: 18 41 |
| Specialist physician visit        | HCFA: 46 39 06 48 |

Table 2. Factor Analysis—Screening Adherence.

| Factor component                      | Factor loading |
|---------------------------------------|----------------|
| Hb1AC test                            | 0.18           |
| Lipid test                            | 0.25           |
| Urine test                            | 0.22           |
| Blood pressure test                   | 0.26           |
| General practitioner visit            | 0.21           |
| Optometrist or Ophthalmologist visit  | 0.12           |
| Specialist physician visit            | 0.13           |
| Factor eigenvalueb                    | 1.10           |

*Varimax rotation was used.
*Satisfies Kaiser criterion for retaining the factor.
chronic renal disease, blindness, and lower extremity complication of T2D.

The left-truncated Cox model, which allows for the identification of intensifier variables as well as their statistical significance (Lanfranchi, Viola, & Nascimento, 2011), calculated over the interval between each individual's age at baseline and exit was used for the study (Allison, 2010). Age was used as a follow-up variable in a left-truncated design so that comparisons of study individuals were performed at identical ages. The advantage of this approach is that it allowed us to account for age, the most important nongenetic risk factor for AD, non-parametrically. All Medicare-based comorbidities were included as time-varying covariates using the respective age of onset of each comorbidity (Allison, 2010). Values for survey-based covariates were taken from the wave on or immediately before the baseline date. Adherence was averaged over the study time period for each individual. SAS software version 9.4 (© SAS Institute Inc., Cary, NC, USA) was used for all analysis.

Results

Summary statistics for the study sample at baseline are provided in Table 3. Of 3,797 individuals newly diagnosed with T2D, 519 (13.66%) were diagnosed with AD over the study time period at an average age of 83.56 (average time to onset of about 8 years). An interesting pattern can be seen when the sample is stratified into adherent/nonadherent subgroups using the three alternative cutoff points (0.2, 0.5, 1.0). Regardless of cutoff point, the adherent group always has a higher proportion of individuals who are (a) White, (b) married, and (c) college-educated, and a lower proportion of individuals with (a) more than four functional limitations, (b) dementia, (c) stroke, (d) myocardial infarction, and (e) congestive heart failure. Somewhat counterintuitively, the adherent group was more likely to have chronic renal disease and lower extremity complications; however, this could be due to the additional physician care required for these conditions.

Cox results are presented in Table 4. Continuous adherence reduces the risk for AD onset by 19% (hazard ratio [HR]: 0.81; 95% confidence interval [CI]: [0.67, 0.97]). The effect is fairly linear with adherence levels of 0.5 and 1.0 reducing the risk by 28% (HR: 0.72; CI: [0.58, 0.89]) and 42% (HR: 0.58; CI: [0.40, 0.83]), respectively. College education reduced the risk of AD onset by 35% (HR: 0.65; CI: [0.45, 0.94]) for all specifications. Reduced functional status increased risk by about 33% (HR: 1.33; CI: [1.08, 1.64]). Only two comorbidity categories had a significant effect: stroke (HR: 1.41; CI: [1.07, 1.84]) and the presence of other dementias (HR: 12.94; CI: [10.38, 16.13]). Although the strong adverse effect of the presence of other dementias is expected due to the phenomenon of multiple dementia (i.e., more than one type of dementia diagnosis present in a single patient) and the difficulty of distinguishing AD from other types of dementia, especially at early stages, the magnitude of the associated HR brings up concerns about the stability of the results. To offset this concern, sensitivity analysis was conducted. First, adherence was included into the Cox model by itself in univariate analysis, then the full analysis was repeated with the dementia variable excluded. Both, coefficient size and level of significance were stable and consistent.

Discussion

Using an HRS-based sample of Medicare beneficiaries, age 66+, newly diagnosed with T2D between 1991 and 2012, we found that adherence to ADA screening guidelines reduced the risk of AD onset by 19% on average. This protective effect increased at higher levels of adherence. The study-wide incidence rate of AD in this population was about 137 in 1,000 individuals. College education was found to be protective at all levels of adherence with the adherent group consistently showing a higher average number of college graduates. This result is consistent with other studies (Freedman, Aykan, & Martin, 2001, 2002; Langa et al., 2008; Manton et al., 2005). Education is hypothesized to reduce AD risk through increasing an individual’s cognitive reserve (Scarmeas, Albert, Manly, & Stern, 2006; Stern, 2006)—that is, a better developed brain can sustain more damage prior to failing. Our findings support this hypothesis and provide evidence for an additional pathway by which education affects AD risk: individuals with college or better education are more likely to engage in health-conscious behavior and take steps to manage their existing chronic diseases that their less educated peers (House, Lantz, & Herd, 2005; Schoeni, Freedman, & Martin, 2009). Four or more limitations in physical function were associated with higher risk of AD onset. A likely pathway is that physical limitations negatively affect the ability to engage in health-conscious behavior such as adherence and exercise (Buchman et al., 2012; Geda et al., 2010; Hamer & Chida, 2009; Liu et al., 2012; Middleton, Barnes, Lui, & Yaffe, 2010). This line of reasoning is supported by our findings as the adherent group contained lower proportions of individuals with four or more functional limitations at all adherence levels. The strong adverse effects associated with stroke and other dementia reflect the close relationships between these conditions and cognitive function: Recent research has shown that an average individual with cognitive impairment usually has more than one contributing condition (Jellinger, 2007; Jellinger & Attems, 2007; Schneider, Arvanitakis, Bang, & Bennett, 2007). Furthermore, the effect of stroke/other dementias on cognition can mask the symptoms of early stage AD.

Cardiovascular diseases such as myocardial infarction and congestive heart failure are suspected risk factors for AD development with common links to inflammatory responses and other metabolic mechanisms (Langa et al., 2008). In our study, we did not find evidence of increased risk of AD associated with these health disorders. This is
### Table 3. Summary Statistics.

|                          | Full sample | Not adherent | Adherent | Not adherent | Adherent | Not adherent | Adherent | Not adherent | Adherent | Not adherent | Adherent |
|--------------------------|-------------|--------------|----------|--------------|----------|--------------|----------|--------------|----------|--------------|----------|
| **Male**                 | 0.46 (0.50) | 0.47 (0.50)  | 0.45 (0.50) | 0.46 (0.50)  | 0.44 (0.50) | 0.45 (0.50)  | 0.47 (0.50) | 0.45 (0.50)  | 0.47 (0.50) | 0.45 (0.50)  | 0.47 (0.50) |
| **White**                | 0.74 (0.44) | 0.72 (0.45)  | 0.75 (0.43) | 0.73 (0.44)  | 0.74 (0.44) | 0.73 (0.44)  | 0.76 (0.42) | 0.73 (0.44)  | 0.76 (0.42) | 0.73 (0.44)  | 0.76 (0.42) |
| **Married**              | 0.56 (0.50) | 0.51 (0.50)  | 0.59 (0.49) | 0.53 (0.50)  | 0.60 (0.49) | 0.55 (0.50)  | 0.60 (0.49) | 0.55 (0.50)  | 0.60 (0.49) | 0.55 (0.50)  | 0.60 (0.49) |
| **College education**    | 0.14 (0.35) | 0.12 (0.32)  | 0.16 (0.37) | 0.12 (0.32)  | 0.18 (0.38) | 0.13 (0.33)  | 0.21 (0.41) | 0.13 (0.33)  | 0.21 (0.41) | 0.13 (0.33)  | 0.21 (0.41) |
| **Adherence (continuous)** | 0.34 (0.62) |              |           |              |          |              |          |              |          |              |          |
| **Adherence (binary ≥ 0.2)** | 0.56 (0.50) |              |           |              |          |              |          |              |          |              |          |
| **Adherence (binary ≥ 0.5)** | 0.38 (0.49) |              |           |              |          |              |          |              |          |              |          |
| **Adherence (binary ≥ 1.0)** | 0.15 (0.36) |              |           |              |          |              |          |              |          |              |          |
| **Functional limitations (four or more)** | 0.37 (0.48) | 0.40 (0.49)  | 0.35 (0.48) | 0.38 (0.49)  | 0.36 (0.48) | 0.38 (0.49)  | 0.36 (0.48) | 0.38 (0.49)  | 0.36 (0.48) | 0.38 (0.49)  | 0.36 (0.48) |
| **Dementia**             | 0.20 (0.40) | 0.22 (0.41)  | 0.18 (0.38) | 0.22 (0.41)  | 0.16 (0.37) | 0.21 (0.41)  | 0.11 (0.32) | 0.21 (0.41)  | 0.11 (0.32) | 0.21 (0.41)  | 0.11 (0.32) |
| **Stroke**               | 0.21 (0.41) | 0.22 (0.41)  | 0.21 (0.41) | 0.22 (0.42)  | 0.20 (0.40) | 0.22 (0.42)  | 0.20 (0.40) | 0.22 (0.42)  | 0.20 (0.40) | 0.22 (0.42)  | 0.20 (0.40) |
| **Myocardial infarction** | 0.17 (0.38) | 0.18 (0.39)  | 0.16 (0.37) | 0.18 (0.38)  | 0.16 (0.37) | 0.17 (0.38)  | 0.16 (0.37) | 0.17 (0.38)  | 0.16 (0.37) | 0.17 (0.38)  | 0.16 (0.37) |
| **Congestive heart failure** | 0.44 (0.50) | 0.45 (0.50)  | 0.43 (0.50) | 0.47 (0.50)  | 0.39 (0.49) | 0.46 (0.50)  | 0.34 (0.47) | 0.46 (0.50)  | 0.34 (0.47) | 0.46 (0.50)  | 0.34 (0.47) |
| **Chronic renal disease** | 0.21 (0.41) | 0.18 (0.39)  | 0.23 (0.42) | 0.19 (0.39)  | 0.25 (0.43) | 0.20 (0.40)  | 0.25 (0.44) | 0.20 (0.40)  | 0.25 (0.44) | 0.20 (0.40)  | 0.25 (0.44) |
| **Blindness**            | 0.02 (0.14) | 0.02 (0.15)  | 0.02 (0.14) | 0.02 (0.14)  | 0.02 (0.15) | 0.02 (0.14)  | 0.02 (0.14) | 0.02 (0.14)  | 0.02 (0.14) | 0.02 (0.14)  | 0.02 (0.14) |
| **Lower extremity complication** | 0.11 (0.32) | 0.09 (0.29)  | 0.13 (0.34) | 0.10 (0.31)  | 0.13 (0.34) | 0.11 (0.31)  | 0.14 (0.35) | 0.11 (0.31)  | 0.14 (0.35) | 0.11 (0.31)  | 0.14 (0.35) |
| **N**                    | 3,797        | 1,658        | 2,139     | 2,354        | 1,443     | 3,232        | 565      | 3,232        | 565      | 3,232        | 565      |
| **Age at baseline**      | 75.31 (7.09) | 76.13 (7.42) | 74.67 (6.76) | 75.90 (7.31) | 74.34 (6.62) | 75.57 (7.19) | 73.83 (6.31) | 75.57 (7.19) | 73.83 (6.31) | 75.57 (7.19) | 73.83 (6.31) |
| **Age at exit**          | 81.37 (7.15) | 81.60 (7.51) | 81.20 (6.85) | 81.62 (7.36) | 80.98 (6.78) | 81.57 (7.23) | 80.26 (6.58) | 81.57 (7.23) | 80.26 (6.58) | 81.57 (7.23) | 80.26 (6.58) |
| **n with Alzheimer's disease** | 519        | 244          | 275       | 359          | 160       | 478          | 41       | 478          | 41       | 478          | 41       |
| **Age at Alzheimer's disease onset** | 83.56 (6.54) | 83.96 (6.98) | 83.21 (6.11) | 83.71 (6.82) | 83.23 (5.87) | 83.68 (6.61) | 82.16 (5.52) | 83.68 (6.61) | 82.16 (5.52) | 83.68 (6.61) | 82.16 (5.52) |
consistent with existing evidence of improved control of cardiovascular risk due to increased use of statins and antihypertensive medications as well as aggressive public health measures aimed at promoting health-conscious behavior (Khachaturian et al., 2006; Langa et al., 2008).

We acknowledge the following limitations: Medicare administrative claims data are not intended for research. However, its use has been validated in the study of many chronic diseases including T2D and its complications (P. L. Hebert et al., 1999), and the algorithm used to identify AD onset from Medicare claims has been used in prior studies (Akushevich et al., 2016). Furthermore, AD presents a unique challenge as in its early stages its symptoms are similar to that of many other dementias. This is complicated by the fact that there is no nonpalliative treatment for AD, so even after a diagnosis is made, there is little cause to return to the physician potentially leading to under-identification of individuals with AD. However, Medicare-based estimates of AD are known to be on the high-end among all data sources used (L. E. Hebert et al., 2010) devaluating the severity of this concern.

**Conclusion**

Although the exact biological mechanism for the development of AD is not known, an extensive body of genetic, pathological, and behavioral factors known to affect AD risk is already identified. Of these risk factors, changes in behavior lend themselves the most to immediate modification. T2D is a serious chronic disease with many epidemiological, cellular, molecular, and metabolic similarities to AD. Furthermore, T2D is strongly associated with other AD risk factors such as cardiovascular disease, obesity, lack of physical activity, and loss of physical function. Improved control of T2D and associated health benefits such as reduced blood glucose levels, cholesterol/blood pressure control, and improved insulin sensitivity lead to a wide range of improvements in health and reduce the risk of AD onset in an otherwise high-risk population. The strong protective effect associated with adherence to T2D screening guidelines identified in this article suggests that public health measures aimed at improving health-related behavior patterns can have an important role to play in the development of strategies of AD prevention.

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**Authors’ Note**

A version of this article was presented at the 2017 Alzheimer’s Association Conference in London, England.

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**Table 4. Effect of Adherence on Risk of Alzheimer’s Disease.**

|                          | Continuous adherence | Adherence ≥ 0.2 | Adherence ≥ 0.5 | Adherence ≥ 1.0 |
|--------------------------|----------------------|----------------|----------------|----------------|
| Adherence                | 0.81*                | 0.82           | 0.72**         | 0.58**         |
|                          | [0.67, 0.97]         | [0.67, 1.01]   | [0.58, 0.89]   | [0.40, 0.83]   |
| Male                     | 1.08                 | 1.08           | 1.07           | 1.08           |
|                          | [0.86, 1.35]         | [0.86, 1.36]   | [0.85, 1.35]   | [0.86, 1.35]   |
| White                    | 0.94                 | 0.94           | 0.93           | 0.93           |
|                          | [0.75, 1.19]         | [0.75, 1.18]   | [0.74, 1.17]   | [0.74, 1.17]   |
| Married                  | 0.91                 | 0.91           | 0.93           | 0.91           |
|                          | [0.73, 1.15]         | [0.73, 1.14]   | [0.74, 1.17]   | [0.72, 1.14]   |
| College education        | 0.65*                | 0.65*          | 0.65*          | 0.65*          |
|                          | [0.45, 0.94]         | [0.45, 0.93]   | [0.45, 0.94]   | [0.45, 0.93]   |
| Functional limitations (4+) | 1.33***              | 1.33***        | 1.34***        | 1.34***        |
|                          | [1.08, 1.64]         | [1.08, 1.64]   | [1.08, 1.65]   | [1.08, 1.65]   |
| Dementia                 | 12.94***             | 13.02***       | 12.89***       | 12.85***       |
|                          | [10.38, 16.13]       | [10.44, 16.23] | [10.35, 16.07] | [10.32, 16.00] |
| Stroke                   | 1.41*                | 1.39*          | 1.42*          | 1.45**         |
|                          | [1.07, 1.84]         | [1.06, 1.82]   | [1.09, 1.86]   | [1.10, 1.89]   |
| Myocardial infarction    | 1.17                 | 1.17           | 1.17           | 1.16           |
|                          | [0.81, 1.68]         | [0.81, 1.68]   | [0.81, 1.69]   | [0.80, 1.67]   |
| Congestive heart failure | 1.20                 | 1.21           | 1.18           | 1.16           |
|                          | [0.94, 1.53]         | [0.94, 1.55]   | [0.92, 1.51]   | [0.91, 1.49]   |
| Chronic renal disease    | 1.30                 | 1.30           | 1.31           | 1.30           |
|                          | [0.95, 1.77]         | [0.95, 1.76]   | [0.96, 1.78]   | [0.96, 1.77]   |
| Blindness                | 1.18                 | 1.16           | 1.16           | 1.15           |
|                          | [0.48, 2.87]         | [0.48, 2.83]   | [0.48, 2.84]   | [0.47, 2.82]   |
| Lower extremity complication | 1.03                 | 1.01           | 1.03           | 1.03           |
|                          | [0.74, 1.44]         | [0.73, 1.41]   | [0.74, 1.44]   | [0.75, 1.45]   |

Note. Numbers presented are hazard ratios with associated 95% confidence intervals.

*p < .05. **p < .01.
Declaration of Conflicting Interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Publication of this article was supported in part by the National Institute on Aging (grants R01-AG046860, R01-AG046860-3S1 and P01-AG043352). The sponsors had no role in design and conduct of the study, collection, management, analysis, interpretation of the data, preparation, review, approval of the manuscript, nor decision to submit the manuscript for publication. The Health and Retirement Study data is sponsored by the National Institute on Aging (grants R01-AG046860, R01-AG046860-3S1 and P01-AG043352). The sponsors had no role in design and conduct of the data, preparation, review, approval of the manuscript, nor decision to submit the manuscript for publication. The Health and Retirement Study data is sponsored by the National Institute on Aging (grant number U01-AG009740) and is conducted by the University of Michigan.

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