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## Peripheral Neuropathy and All-Cause and Cardiovascular Mortality in US Adults

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### Abstract

**Background:** There is growing evidence that peripheral neuropathy (PN) is common even in the absence of diabetes. However, the clinical sequelae of PN have not been quantified in the general population.

**Objective:** We aimed to assess the associations of PN with all-cause and cardiovascular mortality in the general U.S. adult population.

**Design:** Prospective cohort study.

**Setting:** 1999–2004 National Health and Nutrition Examination Survey(NHANES).

**Participants:** 7,137 participants aged 40 years who underwent standardized monofilament testing for PN.

**Measurements:** Cox regression to evaluate the associations of PN with all-cause and cardiovascular mortality after adjustment for demographic and cardiovascular risk factors.

**Results:** The overall weighted prevalence of PN was 13.5%(SE 0.5%) [27.2%(SE 1.3%) in adults with diabetes and 11.6%(SE 0.5%) in adults without diabetes]. During a median of 13 years of follow-up there were 2140 deaths, including 492 due to cardiovascular causes. In adjusted models, PN was significantly associated with all-cause (HR 1.72, 95% CI 1.28–2.30) and cardiovascular mortality (HR 2.04, 95% CI 1.25–3.32) in participants with diabetes. The association of PN with cardiovascular mortality was particularly evident in adults with long-standing diabetes (HR 3.82, 95% CI 2.12–6.88 for diabetes duration 10 years vs <10 years). In participants without diabetes, PN was also significantly associated with both all-cause (HR 1.37, 95% CI 1.21–1.55) and cardiovascular mortality (HR 1.32, 95% CI 1.02–1.72).

**Limitations:** PN defined by monofilament testing only, prevalent cardiovascular disease was self-reported.

**Conclusion:** PN was common and independently associated with all-cause and cardiovascular mortality in the U.S. population, even in the absence of diabetes. These findings suggest that decreased sensation in the foot may be an under recognized risk factor for mortality in the general population.

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## Introduction

Peripheral neuropathy results in decreased lower extremity sensation that can lead to substantial morbidity in affected adults (1, 2). Although most commonly associated with diabetes (3, 4), PN affects adults with impaired glucose tolerance and normoglycemia as well (5, 6).

Adults with diabetes and PN have a higher risk of foot ulcers, major amputation, and falls than adults without PN (7–10). Among adults with diabetes who have PN and a foot ulcer, the relative risk of mortality is more than 2-fold higher than adults without PN and a foot ulcer (11). PN has also been described as an independent risk factor for mortality among adults with diabetes (12, 13). However, prior studies have typically focused on clinical populations and the mortality implications of PN have not been examined in the general population.

The clinical sequelae of PN in the absence of diabetes is poorly defined. PN is independently associated with functional impairments, work disability, and lower limb amputations even after adjusting for the presence of diabetes (14). To our knowledge, there are no studies that have examined the association of non-diabetic PN with mortality.

We aimed to assess the associations of prevalent PN with mortality in the general US adult population using the most recent data available from the National Health and Nutrition Examination Survey (NHANES).

## Methods

### Study population

The National Health and Nutrition Examination Survey (NHANES) are cross-sectional complex survey samples among the U.S. civilian non-institutionalized population conducted by the National Center for Health Statistics (NCHS). Our study included U.S. adults aged 40 years and older who attended the lower extremity disease exam in the NHANES survey cycles 1999–2004 (N = 7902). We excluded participants who were missing covariates of interest (N = 765), for a final sample size of 7137.

The NCHS Institutional Review Board approved the study protocols and informed consent was obtained from all participants.

### Measurement of peripheral neuropathy

PN was assessed by trained technicians using a standard monofilament (5.07 Semmes-Weinstein nylon monofilament mounted on a plastic handle, delivering approximately a 10-gram filament force) to apply slight pressure to the bottom of each participant's each foot on

three sites - plantar-first metatarsal head, plantar-fifth metatarsal head and plantar-hallux (15). If the participant's first response at a site was correct, the test was not repeated at that site. If the participant could not correctly identify where the pressure was applied, the test was repeated for a maximum of three tests per site until a total of two similar responses were obtained. A site was defined as insensate if the participant gave two incorrect or undeterminable responses for that site. PN was defined as having at least one insensate site on either foot.

### Other Variable definitions

Age, sex, race-ethnicity, education, smoking status and drinking status were self-reported by participants. Diabetes was defined as self-reported doctor diagnosed diabetes or HbA1c  $\geq 6.5\%$ . Normoglycemia was defined as HbA1c  $< 5.7\%$ . Body mass index (BMI) was calculated as weight (kilograms) divided by squared height (meters<sup>2</sup>). Hypertension was defined as systolic blood pressure (SBP)  $\geq 140$  mmHg, diastolic blood pressure (DBP)  $\geq 90$  mmHg, or taking blood pressure control medication. Hypercholesterolemia was defined as total cholesterol  $\geq 240$  mg/dL or taking cholesterol control medication. Participants who self-reported doctor diagnosed coronary heart disease, heart attack or stroke were classified as having cardiovascular disease (CVD). Peripheral artery disease (PAD) was defined as left or right ankle brachial index (ABI)  $< 0.9$ . Chronic kidney disease was defined as eGFR  $< 60$  mL/min/1.73m<sup>2</sup> or urine albumin to creatinine ratio  $\geq 30$ .

### All-cause and cardiovascular mortality

NHANES is linked to death certificate records from the National Death Index. The public-use linked mortality file for 1999–2014 NHANES includes follow-up time and underlying cause of death for NHANES adult participants through December 31, 2015 (16). A detailed description of the linkage methodology and analytic guidelines are available on the NCHS data linkage webpage (17). Cardiovascular mortality was defined as any heart disease-related or cerebrovascular disease-related death.

### Statistical analyses

We examined the characteristics of U.S. adults in our study according to both diabetes and PN status. We generated Kaplan-Meier survival curves for all-cause mortality and cardiovascular mortality stratified by diabetes and PN status. We used Cox proportional hazards models to assess the associations of PN with all-cause and cardiovascular mortality in adults with and without diabetes separately. Model 1 was adjusted for age, sex and race-ethnicity. Model 2 was adjusted for all variables in Model 1 as well as other mortality risk factors including education, BMI, smoking status, drinking status, prevalent CVD, hypertension and hypercholesterolemia. We also evaluated the combined association of duration of diabetes and PN status with overall mortality and cardiovascular mortality in participants with diabetes. We then performed a sensitivity analysis assessing the association of PN with all-cause and CVD mortality adjusting for all variables in Model 2 as well as chronic kidney disease (participants with and without diabetes) and retinopathy (participants with diabetes only) separately. We performed an additional sensitivity analysis assessing the association of PN with all-cause and cardiovascular mortality adjusting for all variables in Model 2 among adults with normoglycemia.

We performed all analyses using Stata, version 15.1 (StataCorp) with a P-value less than 0.05 indicating statistical significance. All analyses incorporated sampling weights to obtain unbiased estimates from the complex NHANES design and we used Taylor series (linearization) to estimate standard errors.

## Results

The overall prevalence of PN was 13.5% (SE 0.5%) in the general U.S. adult population aged 40 years or older. The prevalence was 27.2% (SE 1.3%) in adults with diabetes and 11.6% (SE 0.5%) in those without diabetes. Adults with PN were older, more frequently male, and had lower levels of education compared to participants without PN (Table 1). Participants with PN also had higher BMI, were more commonly former or current smokers, and had a higher prevalence of hypertension, hypercholesterolemia, and PAD (Table 1). Prevalent CVD was higher among adults with *versus* without PN in both the diabetes (30.6% vs. 19.0%) and no diabetes (16.6% vs. 8.3%) groups.

Over a median follow-up of 13 years, there were 2140 total deaths and 492 deaths due to cardiovascular causes. The incidence rate (per 1000 person-years) of all-cause mortality through 2015 (maximum follow-up, 17 years) was 58.0 (95% CI 48.8–69.0) in adults with diabetes and PN, 27.4 (95% CI 23.7–31.7) in adults with diabetes and no PN, 34.3 (95% CI 30.3–38.8) in adults with no diabetes and PN, and 13.0 (95% CI 12.2–14.0) in adults with no diabetes and no PN (Table 2). The leading cause of death among participants with diabetes was cardiovascular disease (31% of total deaths), whereas the leading cause of death among participants without diabetes was malignant neoplasms (27% of total deaths) (Appendix Table 1). In crude Kaplan-Meier analyses, the risk of all-cause and cardiovascular mortality was highest among adults with diabetes and PN, but PN was also associated with mortality in the absence of diabetes (Figure 1). The risk of all-cause mortality among adults with PN in the absence of diabetes was nearly equivalent to that for adults with diabetes but no PN (Figure 1A).

After adjusting for age, sex, and race-ethnicity, PN was significantly associated with all-cause and CVD mortality in participants with and without diabetes (Table 2, Model 1). After adjusting for additional risk factors including prevalent CVD, PN was significantly associated with all-cause (HR 1.72, 95% CI 1.28–2.30) and cardiovascular mortality (HR 2.04, 95% CI 1.25–3.32) in participants with diabetes (Model 2). The association of PN with all-cause and cardiovascular mortality among participants with diabetes was strongest for those participants with long-standing diabetes (i.e.  $\geq 10$  years) (Table 3). In participants without diabetes, PN was significantly associated with both all-cause (HR 1.37, 95% CI 1.21–1.55) and cardiovascular mortality (HR 1.32, 95% CI 1.02–1.72) in Model 2. Our results did not substantially change after additionally adjusting for chronic kidney disease or retinopathy (Appendix Table 2).

In a sensitivity analysis limited to adults with normoglycemia (Appendix Table 3), the risk-adjusted association of PN with all-cause mortality persisted (HR 1.37, 95% CI 1.18–1.60). The association of PN with cardiovascular mortality was significant after adjusting for age,

sex, and race-ethnicity (HR 1.39, 95% CI 1.07–1.83), but was attenuated after further adjusting for additional risk factors (HR 1.28, 95% CI 0.94–1.74).

## Discussion

We found that the prevalence of PN in the U.S. population was substantial, even among adults without diabetes. PN was associated with both all-cause and cardiovascular mortality in adults with and without diabetes, and these associations persisted even after adjustment for prevalent cardiovascular disease and other mortality risk factors. Among adults with diabetes, the association of PN with mortality was strongest for those with long-standing diabetes  $\geq 10$  years. Overall, our data suggest that PN is a marker of increased mortality risk among U.S. adults.

We found that the prevalence of PN was 27.2% in U.S. adults aged  $\geq 40$  years with diabetes and 11.6% in U.S. adults aged  $\geq 40$  years without diabetes, equivalent to 35 million adults based on the 2020 U.S. Census. These estimates are consistent with previously published reports (3, 4, 18). While diabetes is a well-established risk factor for PN (19–21), the high prevalence of PN among adults without diabetes is notable.

The etiology of PN in the absence of diabetes is unclear. There is some evidence to suggest that adults with PN who do not have diabetes may have impaired glucose tolerance or prediabetes (5, 6, 22). However, we found a persistent association of PN with all-cause mortality among adults with normoglycemia. Prior studies have reported an association of normoglycemic PN with features of metabolic syndrome (other than hyperglycemia) (23, 24), suggesting that chronic metabolic derangements may play a role in the pathogenesis of PN (25). We recently reported a significant association of body mass index and hypertension with PN among adults both with and without diabetes (Hicks et al., *Under review*). While diabetes is a well-established risk factor for PN, our data suggest that the prevalence of PN among adults without diabetes is substantial and may be an under-recognized risk factor for mortality.

The risks of all-cause and cardiovascular mortality were significantly higher for adults with diabetes and PN compared to those without PN in our study. Adults with diabetes are known to have a 2–4 times higher cardiovascular risk compared to adults without diabetes (26). However, the specific mortality associated with PN has not previously been described. Previous studies have reported that adults with diabetes and neuropathic sequelae, such as foot ulcers, have a higher risk of death than adults with diabetes who do not have neuropathic sequelae (27–30). In the past, these elevated mortality rates have largely been attributed to subsequent major amputation and/or a higher prevalence of macrovascular atherosclerotic disease in affected patients (29, 31). As a result, it is possible that elevated mortality among adults with PN is partially attributable to infected foot ulcers and/or subsequent major amputation. However, we also found that the risk of cardiovascular mortality remained higher among adults with diabetes and PN even after adjusting for cardiovascular risk factors, prevalent cardiovascular disease, and PAD. The presence of PN may portend a higher risk of concomitant cardiac autonomic neuropathy or other unmeasured conditions. PN confers significantly higher risk of cardiac autonomic

neuropathy among adults with diabetes (32). We have previously reported elevated high-sensitivity troponin T, brain natriuretic peptide levels, and kidney biomarkers among adults with PN (Hicks et al., *In press*), suggesting that the presence of PN may reflect systemic subclinical microvascular disease (33, 34). Our study contributes to the growing body of literature supporting the concept that PN is associated with substantial clinical sequelae.

The association of PN with mortality was highest among adults with long-standing diabetes. Adults with diabetes  $\geq 10$  years in duration and PN had a 2.4-fold higher risk of all-cause mortality and a 3.8-fold higher risk of cardiovascular mortality than adults with diabetes  $< 10$  years duration and no PN. Diabetes duration is a known risk factor for PN (35, 36) and cardiovascular mortality (37). Consistent with this notion, we found that the risk of cardiovascular mortality was 1.6-times higher among adults with diabetes  $\geq 10$  years duration and no PN, but that this risk more than doubled (HR 3.8) among adults with long-standing diabetes and PN.

The risk of all-cause and cardiovascular mortality was also significantly higher for adults with *versus* without PN in the absence of diabetes. Even after adjusting for prevalent cardiovascular disease and other mortality risk factors, the risk of death associated with PN was more than 30% higher in the non-diabetic population. There is a known association of PN with cancer related to the neurotoxic effects of some chemotherapies (38), although a history of cancer was rare in this population-based study. We also found an association of PN with cardiovascular mortality. Indeed, we found that PN in the absence of diabetes conferred approximately the same overall and cardiovascular mortality risk as compared to a diagnosis of diabetes but no PN. We also found an association of PN with mortality among adults with normoglycemia, suggesting that hyperglycemia is not the only etiology for the disease. PN assessed by monofilament testing appears to be an unrecognized marker for mortality risk.

The limitations of our study include self-report of prevalent cardiovascular disease. We also do not have data on non-diabetic etiologies of PN (e.g. toxin exposures, autoimmune disease, vitamin deficiencies, etc.) or the duration of disease. PN was assessed using a cross-sectional evaluation of NHANES participants, so we could not evaluate long-standing vs. shorter term PN. Finally, we did not have electromyography and nerve conduction tests to diagnose PN. NHANES did not collect data on participant symptoms using symptom-based screening instruments (39, 40), and did not evaluate participants using a tuning fork or vibration perception test, which may be more sensitive than monofilament testing (41). However, PN was assessed using a 10-g standard monofilament test, which reflects clinical practice for PN screening and is the recommended test to diagnose PN in its more severe form, loss of protective sensation (42). As such, it is important to distinguish that we found an association of PN in the form of impaired sensation with all-cause and cardiovascular mortality.

Strengths of our study include the large sample size and collection of major risk factors in a standardized fashion by trained personnel. NHANES data are representative of the U.S. population, meaning that our findings are generalizable to U.S. adults  $\geq 40$  years of age. BMI, hypertension, PAD, and chronic kidney disease were all based on standard

measurements performed in NHANES, and diabetes was defined based on hemoglobin A1c in participants without an established diagnosis of diabetes. Finally, mortality was identified using the National Death Index, which allowed for accurate mortality risk estimates.

In conclusion, the prevalence of PN as assessed by monofilament testing is substantial in the U.S. population, even among adults without diabetes. PN was independently associated with all-cause and cardiovascular mortality regardless of diabetes status and other cardiovascular risk factors. These findings suggest that decreased sensation in the foot may be an under recognized risk factor for mortality in the general population.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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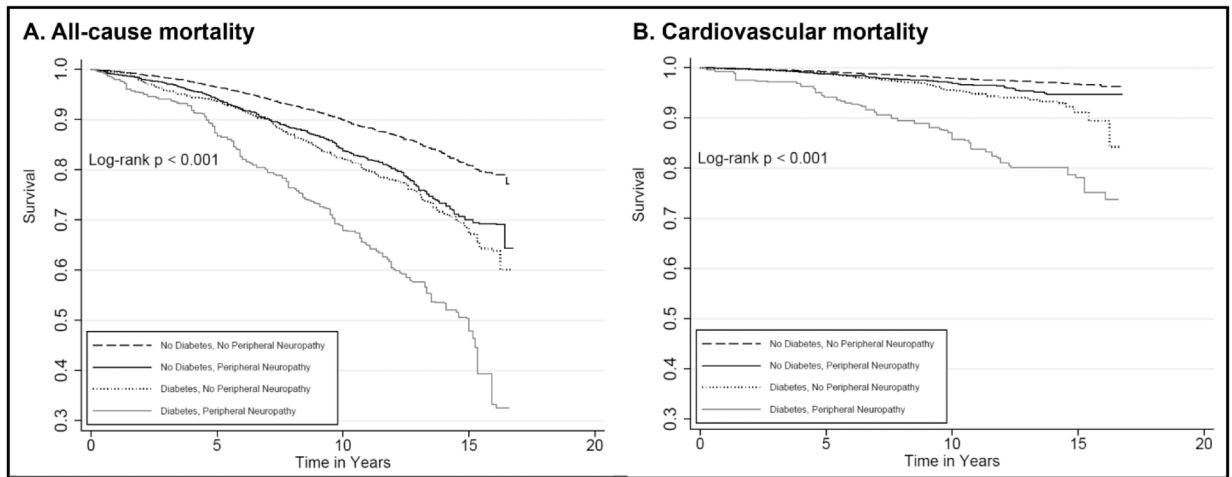
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**Figure 1.** Kaplan-Meier (crude) survival curves according to peripheral neuropathy and diabetes status for all-cause mortality (Panel A) and cardiovascular mortality (Panel B), U.S. Adults Aged 40 years, NHANES, 1999–2004

**Table 1.**

Characteristics of U.S. Adults Aged 40 years (% , SE) According to Diabetes and Peripheral Neuropathy (PN) Status, NHANES, 1999–2004

	No Diabetes		Diabetes	
	No PN	PN	No PN	PN
Unweighted N	5037	905	838	357
	% (SE)	% (SE)	% (SE)	% (SE)
Mean age, years	54.9 (0.2)	63.3 (0.7)	60.3 (0.5)	64.3 (1.0)
Age in years				
40–49	40.7 (1.1)	19.0 (2.1)	20.1 (1.9)	12.2 (2.8)
50–59	28.6 (0.9)	22.9 (1.7)	29.1 (2.2)	22.1 (3.0)
60–69	16.2 (0.7)	21.9 (1.6)	28.2 (1.8)	28.1 (3.1)
70–79	10.6 (0.4)	22.2 (1.6)	17.1 (1.5)	26.9 (3.1)
80+	4.0 (0.3)	13.9 (1.1)	5.5 (0.6)	10.7 (1.7)
Male	45.5 (0.6)	61.1 (1.7)	47.9 (2.3)	65.5 (3.6)
Race-ethnicity				
Non-Hispanic White	80.7 (1.4)	80.6 (1.8)	63.8 (3.4)	69.6 (3.9)
Non-Hispanic Black	7.8 (0.8)	9.2 (1.2)	13.8 (1.9)	13.2 (2.3)
Hispanic	3.9 (0.8)	5.2 (1.3)	7.5 (2.5)	2.8 (1.3)
Other	7.7 (0.8)	5.1 (0.9)	14.9 (1.9)	14.4 (3.1)
Education				
Less than high school	17.0 (0.8)	27.2 (2.3)	30.7 (1.9)	34.9 (3.7)
High school or equivalent	26.3 (0.9)	26.4 (2.0)	24.4 (1.9)	31.0 (3.3)
College and above	56.8 (1.3)	46.3 (2.6)	44.9 (2.2)	34.2 (3.7)
BMI (kg/m <sup>2</sup> )				
<25.0	31.7 (1.2)	25.9 (1.7)	16.4 (1.9)	13.5 (2.5)
25.0–29.9	38.5 (0.9)	39.4 (2.5)	32.9 (2.1)	32.5 (3.6)
30.0	29.7 (1.0)	34.7 (2.8)	50.6 (2.8)	54.0 (3.6)
Smoking status				
Never	47.1 (1.0)	43.1 (2.4)	46.7 (2.9)	44.6 (3.6)
Former	32.1 (1.0)	38.8 (2.2)	34.9 (2.5)	38.1 (4.0)
Current	20.7 (0.7)	18.2 (1.8)	18.4 (1.6)	17.4 (3.1)
Drinking status				
Never	11.2 (1.1)	15.5 (1.7)	18.3 (1.8)	20.9 (2.6)
Former	19.4 (1.2)	24.6 (2.0)	34.3 (2.2)	36.9 (4.3)
Current	69.4 (1.8)	59.9 (2.4)	47.4 (2.8)	42.2 (4.6)
Cardiovascular disease	8.3 (0.5)	16.6 (1.5)	19.0 (1.6)	30.6 (3.8)
Hypertension	39.0 (1.1)	52.8 (2.3)	63.4 (2.1)	71.1 (3.2)
Hypercholesterolemia	33.2 (0.9)	34.6 (2.0)	49.2 (2.5)	46.3 (4.1)
Peripheral artery disease <sup>a</sup>	4.2 (0.3)	8.3 (1.0)	7.6 (1.5)	17.7 (3.3)
Cancer	10.6 (0.4)	17.0 (1.5)	14.6 (1.6)	19.5 (2.8)
Hemoglobin A1c, % (SE)	5.4 (0.01)	5.5 (0.01)	7.4 (0.07)	7.6 (0.13)

<sup>a</sup>In the sub-population with PAD data (N=6101)

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Hazard ratios (95% CIs) of Peripheral Neuropathy with All-cause and Cardiovascular Mortality in U.S. Adults Aged 40 years, NHANES, 1999–2004

**Table 2.**

	No Diabetes			With Diabetes				
	Events/N	Incidence Rate per 1000 (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Events/N	Incidence Rate per 1000 (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
All-cause mortality								
No PN	1186/5037	13.0 (12.2–14.0)	1 (Ref)	1 (Ref)	314/838	27.4 (23.7–31.7)	1 (Ref)	Model 2 1 (Ref)
With PN	430/905	34.3 (30.3–38.8)	1.40 (1.26–1.56)	1.37 (1.21–1.55)	210/357	58.0 (48.8–69.0)	1.79 (1.36–2.36)	1.72 (1.28–2.30)
Cardiovascular mortality								
No PN	241/5037	2.4 (2.0–2.8)	1 (Ref)	1 (Ref)	85/838	7.7 (5.9–10.2)	1 (Ref)	1 (Ref)
With PN	104/905	7.3 (5.8–9.3)	1.40 (1.09–1.79)	1.32 (1.02–1.72)	62/357	19.8 (14.5–27.7)	2.11 (1.35–3.29)	2.04 (1.25–3.32)

Model 1: Adjusted for age, sex, and race-ethnicity

Model 2: Adjusted for variables in Model 1 plus education, BMI, smoking status, drinking status, cardiovascular disease, hypertension and hypercholesterolemia

**Table 3.** Hazard Ratios (95% CIs) of All-cause and Cardiovascular Mortality with Duration of Diabetes and Peripheral Neuropathy in U.S. Adults Aged 40 years with Diabetes, NHANES, 1999–2004

	PN	Events/N	Incidence Rate per 1000 (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
All-cause mortality					
Diabetes duration <10 years	No	178/555	22.0 (18.2–26.8)	1 (Ref)	1 (Ref)
Diabetes duration <10 years	Yes	87/172	49.3 (38.4–63.6)	1.80 (1.25–2.57)	1.62 (1.10–2.39)
Diabetes duration 10 years	No	134/281	39.4 (31.8–49.1)	1.50 (1.14–1.99)	1.37 (1.02–1.84)
Diabetes duration 10 years	Yes	121/180	68.3 (53.3–87.4)	2.53 (1.84–3.49)	2.42 (1.75–3.33)
Cardiovascular mortality					
Diabetes duration <10 years	No	45/555	5.5 (3.8–8.3)	1 (Ref)	1 (Ref)
Diabetes duration <10 years	Yes	21/172	11.3 (6.5–21.4)	1.57 (0.67–3.69)	1.40 (0.58–3.33)
Diabetes duration 10 years	No	39/281	12.3 (8.5–18.4)	1.87 (1.02–3.44)	1.56 (0.85–2.86)
Diabetes duration 10 years	Yes	46/180	29.5 (19.9–44.8)	4.13 (2.26–7.56)	3.82 (2.12–6.88)

Model 1: Adjusted for age, sex and race-ethnicity

Model 2: Adjusted for variables in Model 1 plus education, BMI, smoking status, drinking status, cardiovascular disease, hypertension and hypercholesterolemia