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Diabetes and fracture risk in older U.S. adults☆

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ABSTRACT

Objective: We examined the diabetes–fracture relationship by race/ethnicity, including the link between pre-diabetes and fracture.
Research design and methods: We used Medicare- and mortality-linked data for respondents aged 65 years and older from the third National Health and Nutrition Examination Survey (NHANES III) and NHANES 1999–2004 for three race/ethnic groups: non-Hispanic whites (NHW), non-Hispanic blacks (NHB), and Mexican Americans (MA). Diabetes was defined as diagnosed diabetes (self-reported) and diabetes status: diagnosed and undiagnosed diabetes (positive diagnosis or hemoglobin A_{1c} (A1C) ≥ 6.5%); pre-diabetes (no diagnosis and A1C between 5.7% and 6.4%); and no diabetes (no diagnosis and A1C < 5.7%). Non-skull fractures (n = 750) were defined using published algorithms. Hazards ratios (HRs) were calculated using Cox proportional hazards models.
Results: The diabetes–fracture relationship differed significantly by race/ethnicity ($p_{interaction} < 0.05$). Compared to those without diagnosed diabetes, the HRs for those with diagnosed diabetes were 2.37 (95% CI 1.49–3.75), 1.87 (95% CI 1.02–3.40), and 1.22 (95% CI 0.93–1.61) for MA, NHB, and NHW, respectively, after adjusting for significant confounders. HRs for diagnosed and undiagnosed diabetes were similar to those for diagnosed diabetes alone. Pre-diabetes was not significantly related to fracture risk, however. Compared to those without diabetes, adjusted HRs for those with pre-diabetes were 1.42 (95% CI 0.72–2.81), and 1.20 (95% CI 0.96–1.51) for MA and NHW, respectively. There were insufficient fracture cases to examine detailed diabetes status in NHB.
Conclusions: The diabetes–fracture relationship was stronger in MA and NHB. Pre-diabetes was not significantly associated with higher fracture risk, however.

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1. Introduction

Diabetes has been linked to an increased risk of fracture [1–14], but many aspects of this relationship remain unclear. For example, few previous studies have examined the diabetes–fracture relationship in race/ethnic groups other than Caucasians [4,6,7], despite the higher prevalence of diabetes in many nonwhite groups [15]. There are also conflicting data regarding the relationship between pre-diabetes and fracture risk, as it has been associated with a significantly lower risk in some [9,11], but not all [5,6,12,16] studies published to date.

We used linked Medicare and mortality data for respondents age 65 years and older from the third National Health and Nutrition Examination Survey (NHANES III) and NHANES 1999–2004 to address these data gaps. We examined differences in the diabetes–fracture relationship by race/ethnicity for three groups: non-Hispanic whites (NHW), non-Hispanic blacks (NHB), and Mexican Americans (MA). We also assessed the relationship between pre-diabetes and fracture risk after using data on diagnosed diabetes and whole blood hemoglobin A_{1c} (A1C) to classify respondents as having diabetes, pre-diabetes, or no diabetes. Finally, we examined the relationship by diagnosed diabetes without regard to A1C values.

2. Research design and methods

2.1. Sample

The baseline data for this study came from NHANES III (1988–1994) and NHANES 1999–2004, which were conducted by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, to assess the health and nutritional status of a large representative sample of the non-institutionalized, civilian population of the U.S. All procedures in each NHANES were approved by the NCHS Ethics Review Board, and written informed consent was obtained from all subjects [17,18]. In each NHANES, data were collected via household interviews and direct standardized physical examinations conducted in specially equipped mobile examination centers [17,18].

☆ The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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NHANES III and NHANES 1999–2004 were designed to provide reliable estimates for three race/ethnic groups: NHW, NHB, and MA. Race and ethnicity were self-reported in both surveys.

Both surveys were linked with mortality files created by NCHS and with Medicare enrollment and claims records in order to have a longitudinal follow-up of the survey participants. Vital status of study participants through 2007 was determined from the restricted access versions of the NHANES III and NHANES 1999–2004 Linked Mortality Files [19].

Medicare enrollment and utilization data were available for NHANES respondents who agreed to provide personal identification [19]. Medicare claims data were provided from respondents who participated in fee-for-service care only from 1991 through 2007 for NHANES III and for 1999–2007 for NHANES 1999–2004. A list of the Medicare files used in the present study is provided in Supplementary Appendix 1.

The analytic sample in this study was restricted to respondents aged 65 years and older at the time of their NHANES interview at baseline because Medicare provides comprehensive health care for roughly 98% of the US population in this age range. Table A in Supplementary Appendix 2 shows the number of persons excluded from the analytic sample and reasons for exclusion for each survey. After excluding a total of 2274 individuals, 2978 (57%) of the original 5252 eligible interviewed individuals from NHANES III were included in the final analytic sample. After excluding a total of 2295 individuals, 2054 (47%) of the original 4349 eligible interviewed individuals from NHANES 1999–2004 were included in the final analytic sample. Approximately 18% of the eligible interviewed sample from both surveys was excluded because they did not receive physical examinations; this nonresponse was addressed by inclusion of nonresponse adjustments in the creation of sample weights for the examined sample. Roughly 13% of the eligible sample was excluded due to prior fracture at baseline. A relatively large number of respondents in NHANES 1999–2004 also were excluded because they were either ineligible for Medicare linkage[1] (10% excluded) or were enrolled in an HMO at baseline (12% excluded). Descriptive characteristics and risk factors were compared between the analytic sample and excluded respondents to assess possible nonresponse bias. The excluded respondents were older, more likely to be women, had higher body mass index (BMI), and self-rated their health as fair or poor than respondents who were included. There were no differences in self-reported diabetes diagnosis between included and excluded respondents, however.

2.2. Fracture case identification

Respondents with fractures at skeletal sites other than the skull were identified using an approach based on previously published methods [20–22]. Skull fractures were not included since they are unlikely to be due to osteoporosis [23]. Cases were defined using relevant International Classification of Disease (ICD), Healthcare Common Procedure Coding System (HCPCS) or Current Procedural Terminology (CPT) codes for the years 1991–2007 [24,25]. Respondents with codes indicating care of previous fracture or other bone diseases, neoplasm or hip arthroplasty for arthritis were excluded from the analyses. Details regarding the definition of cases from Medicare records, including the specific codes, are provided in Supplementary Appendix 1 or have been published previously [26]. Cause of death information from the NHANES Linked Mortality Files was also used to identify hip fracture cases. Specifically, decedents with an ICD-9 code 820 or ICD-10 code S72.0–S72.2 listed anywhere on the death certificate were defined as hip fracture cases.

[1] See Table A in Supplement 2 for ineligibility criteria.

2.3. Variables

2.3.1. Diabetes status

Diabetes status was based on self-reported physician's diagnosis of diabetes and on A1C levels in the main analyses in the present study. A1C was measured at the University of Missouri—Columbia in both surveys using high-performance liquid chromatography performed on instruments certified by the National Glycohemoglobin Standardization Program [27,28]. A1C results were standardized to the reference method used for the Diabetes Control and Complications Trial [29]. Fasting plasma glucose (FPG) was used to define diabetes for a sensitivity analysis in non-Hispanic whites only because it was only available for a subsample whose blood was drawn in the morning, and there were insufficient fracture cases in this subsample to permit analyses in the other race/ethnic groups. Plasma glucose was measured at the University of Missouri—Columbia in both surveys using the enzyme hexokinase [27,28].

Two definitions of diabetes status were used when examining fracture risk. Diagnosed diabetes (yes vs. no) was based on the self-reported questionnaire item only. Women who reported diagnosis of diabetes during pregnancy only were not considered to have diagnosed diabetes. The more detailed definition of diabetes status used in the main analyses combined self-reported diagnosis and A1C values as follows: a) diabetes (diagnosed and undiagnosed): self-reported diagnosis or A1C ≥ 6.5%; b) prediabetes: no self-reported diagnosis and A1C between 5.7% and 6.4%; c) no diabetes: no self-reported diagnosis and A1C < 5.7%. The detailed definition used in the sensitivity analysis based on FPG used the following criteria: a) diabetes: self-reported diagnosis or FPG ≥ 126 mg/dL; b) prediabetes: no self-reported diagnosis and FPG between 100 and 125 mg/dL; c) no diabetes: no self-reported diagnosis and FPG < 100 mg/dL. The sensitivity analyses were limited to NHW whose blood was drawn in the morning after fasting between 8 and 24 h.

Some additional diabetes-related variables were explored to assess their role in the observed race/ethnic differences in the diabetes–fracture relationship. Undiagnosed diabetes was defined as having A1C ≥ 6.5% but no self-reported diabetes. Lower glycemic level was defined for those with a diabetes diagnosis as having A1C < 7.0% [30,31]. Other variables related to diabetes status were obtained by interview and included self-reported age at diagnosis, duration of diabetes, and diabetes treatment. Duration of diabetes was calculated by subtracting age at diagnosis from age at baseline. Diabetes treatment was based on questionnaire items regarding current diabetes medication use. Responses were categorized as insulin only, oral medications only, insulin plus oral medication, and neither insulin or oral medication.

2.3.2. Confounding or exclusion variables

Only variables that were measured comparably in the two surveys were used. Variables that were measured during the physical examination included body weight and height, which were used to calculate body mass index (BMI, equal to body weight (kilograms) divided by height (meters squared)). Variables obtained by interview at baseline included age, self-reported race–ethnicity, self-reported hip, wrist or spine fracture, self-reported lower extremity amputations, smoking status (ever vs. never), self-reported physical activity level compared to others of the same age and sex (same, higher, lower), self-rated health status (excellent/very good/good versus fair/poor), maternal history of hip fracture, hospital stays in the past year (none versus ≥ 1), chronic conditions (self-reported diagnosis of heart attack, congestive heart failure, stroke, emphysema, or cancer), doctor visits in the past year (none, 1–3, ≥4), time since last doctor visit (<1 year versus ≥1 year or never), education (<12 years, 12 years, >12 years), alcohol use (consume ≥ 3 drinks versus <3 drinks per drinking occasion), current glucocorticoid use, and poverty income ratio. Poverty income ratio is based on the number of family members and the annual family income and is calculated using poverty thresholds from the US Census Bureau.