



# Falls, physical limitations, confusion and memory problems in people with type II diabetes, undiagnosed diabetes and prediabetes, and the influence of vitamins A, D and E



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## ABSTRACT

**Aims:** To examine the association between type II diabetes, prediabetes and undiagnosed diabetes with falls, physical limitations, confusion and memory problems, and to evaluate the effects of vitamins A, D and E levels on the associations.

**Methods:** Data from 37,973 participants of the National Health and Nutrition Examination Survey was analyzed.

**Results:** The participants' mean age was  $46 \pm 17$  years, 20% had diabetes of which 17% were unaware of their condition (undiagnosed diabetes), and 21% had prediabetes. Diabetes was significantly associated with falls, difficulties in stooping, crouching, kneeling, completing house chores, getting in and out bed, standing and sitting for long periods, reaching over head, grasping, holding objects, and attending social events. The association between diabetes and confusion or memory problems was stronger for those diagnosed before age 40. Memory problems were reported only by people with diabetes with lower vitamin D levels. Vitamin A and E levels did not modify the association between diabetes and falls or any of the physical functions, confusion or memory problems. Prediabetes was only associated with difficulty standing for long periods.

**Conclusions:** Diabetes was associated with falls, difficulties in physical functioning and attending social events. Vitamin D levels modified the effects on confusion and memory problems.

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## 1. Introduction

Diabetes is “a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both” (Liddle & Gilleard, 1995). Type II diabetes is associated with falls and faster decline in physical and cognitive functions due to neuropathy (Hausdorff, Rios, & Edelberg, 2001; Marks, 2014; Vinik, Vinik, Colberg, & Morrison, 2015). Furthermore, diabetes leads to an unfavorable environment for the muscles affecting physical function, mobility and falls risk. Insulin resistance is a key accelerator of loss of muscle mass and function (Miller, Lui, Perry, Kaiser, & Morley, 1999; Rodríguez-Saldaña et al., 2002). Insulin stimulates glucose uptake and metabolism maintaining glucose homeostasis. Skeletal muscles are the primary site of glucose disposal.

Insulin resistance in skeletal muscles is a major factor in diabetes. Muscles are also affected by the availability of vitamin D, which supports the function of type II muscle fibers, preserving muscle strength and reducing functional decline and falls. Low vitamin D levels are also associated with cognitive decline (Soni et al., 2012).

Loss of muscle mass (sarcopenia), decreased strength and falls are also associated with increased oxidative stress. Therefore, vitamins with antioxidant properties such as vitamins A and E may be protective to muscle health (Cerullo, Gambassi, & Cesari, 2012; Khor, Abdul Karim, Wan Ngah, Mohd Yusof, & Makpol, 2014). Vitamin E levels are associated with strength and frailty (Ble et al., 2006; Cesari et al., 2004). Antioxidant mixtures containing vitamins A and E, zinc, selenium and rutin were found to increase muscle anabolic response in animal models (Marzani et al., 2008). As antioxidant enzymes and potent signaling molecule, vitamins A and E are also thought to have an important role in maintaining cognitive function (Morris, Evans, Bienias, Tangney, & Wilson, 2002; Olson & Mello, 2010).

Little is known about which specific abilities are affected by diabetes, and studies evaluating large, representative samples are needed. Therefore, the objective of this study was to evaluate the association between diabetes, pre-diabetes and undiagnosed diabetes

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with falls and specific physical limitations, confusion or memory problems in a large sample, and to identify if vitamins A, D and E levels affect the associations.

## 2. Subjects

A total of 58,126 participants of all ages of the National Health and Nutrition Examination Survey (NHANES) from the 1999 to 2012 had data on diabetes. Among them, 39,019 aged 20 years and older were interviewed about physical functions, confusion and memory problems. After exclusion of participants with missing data (1,049), the final sample included 37,973 subjects. NHANES protocols were approved by the institutional review boards of the NCHS and CDC, and informed consent was obtained from all participants.

## 3. Materials and methods

### 3.1. Data source

The NHANES is an ongoing cross-sectional survey of the US non-institutionalized civilian population selected using a complex multistage sampling design to derive a representative sample of the US population. It is conducted yearly by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). Two-year data cycles were combined for analysis as per the National Center for Health Statistics recommendations.

### 3.2. Diabetes, undiagnosed diabetes, and pre-diabetes

Participants were classified as having diabetes if they answered yes to the question: "Other than during pregnancy, have you ever been told by a doctor or health professional that you had diabetes or sugar diabetes?", and presented a fasting plasma glucose  $\geq 126$  mg/dl, any random glycaemia  $\geq 200$  mg/dl, or glycohemoglobin  $\geq 6.5\%$ . Participants were classified as having undiagnosed diabetes if they answered no to the same question, but presented a fasting plasma glucose  $\geq 126$  mg/dl, any random glycaemia  $\geq 200$  mg/dl, or glycohemoglobin  $\geq 6.5\%$ . Participants were classified as having pre-diabetes if they answered no to the same question and presented a fasting plasma glucose between 100 and 126 mg/dl, or glycohemoglobin between 5.7 and 6.5%.

### 3.3. Physical functioning, confusion or memory problems, and falls

Data on physical functioning, confusion or memory problems were collected during home visits using a computer-assisted personal interviewing system. Participants were classified as having physical limitations if they reported at least "some difficulty" when walking for a quarter mile without using any assistive device, or when stooping, crouching, or kneeling, or in completing house chores, getting in and out bed, standing or sitting for long periods, reaching over head, grasping/holding objects, or attending social events. Participants were classified as having confusion or memory problems if they answered yes to the question: "Are you limited in any way because of difficulty remembering or because you experience periods of confusion". The NHANES Balance questionnaire available from 1999 to 2004 included data on falls in previous year for the participants aged 40 years and older. The question used to assess history of falls was: "Have you had difficulty with falling during the past 12 months?".

### 3.4. Covariates

Demographic characteristics including age, gender, race/ethnicity, education level, family income, cigarette smoking, were obtained from the NHANES survey. Height and weight were measured in a mobile examination center. Body mass index (BMI) was calculated as

weight in kilograms divided by height in meters squared, and classified as underweight  $< 18.5$  kg/m<sup>2</sup>, normal 18.5–24.9 kg/m<sup>2</sup>, overweight 25–29.9 kg/m<sup>2</sup>, or obese  $\geq 30$  kg/m<sup>2</sup>. Total cholesterol was enzymatically measured in serum using the Roche Hitachi 717 and 912. Family income to poverty ratio was adjusted for family size, year and state. Cigarette smoking status was determined using the question "Have you smoked at least 100 cigarettes in your life?".

Health conditions were ascertained based on the question: "Has a doctor or other health professional ever told you that you have diabetes, arthritis, cardiomyopathies (congestive heart failure, coronary heart disease, and/or history of heart attack), stroke, cancer, thyroid or liver disease?" Each condition was asked about separately. Hypertension was defined by self-report or by a mean systolic blood pressure  $> 140$  mmHg on 4 measurements on 2 separate occasions. Serum vitamins A and E were measured using high performance liquid chromatography with photodiode array detection, and serum vitamin D was assayed using the Diasorin (formerly Incstar) 25-OH-D method. Serum vitamins A and E were measured in NHANES for the years 1999 to 2006, and serum vitamin was measured from 2001 to 2005.

### 3.5. Statistical analysis

All analyses were performed in STATA (Version 11, STATA Corporation, College Station, TX, USA), and p-values  $< 0.05$  were considered statistically significant. NHANES sampling weights and STATA survey commands, taking into account the multistage and complex survey design, were used in all procedures to adjust for unequal selection probabilities, non-responses, over-sampling, post-stratification, and sampling errors, so that estimates were nationally representative.

Descriptive analyses were performed, and p-values for differences in proportions or means by diabetes/prediabetes status were calculated using chi-square test for the categorical variables and Student's t-test for the continuous variables. Multivariate logistic regression analysis was performed while adjusting for age, gender, race/ethnicity, family income to poverty ratio, education level, smoking, BMI, hypertension, arthritis, cardiomyopathies, stroke, comorbidities, glycohemoglobin and total cholesterol. Effect modification by serum vitamins A, D and E on the association between diabetes status and the outcomes was investigated by including the interaction or product term in the models. Stratified analyses were subsequently performed at each level of the significant modifying variables. Afterwards, the association between specific physical function limitations, confusion or memory problems, and falls in the previous year among participants with diabetes or prediabetes was assessed adjusting for the same covariates, and vitamin levels were tested for effect modification.

## 4. Results

Table 1 presents the participants' characteristics ( $n = 37,973$ ). The mean (SD) age was  $46 \pm 17$  years; 52% were women; 70% were non-Hispanic Whites; 20% had type II diabetes ( $n = 7,532$ ) of which 17% were unaware of their condition (undiagnosed diabetes,  $n = 1,280$ ), and 21% had prediabetes ( $n = 7,933$ ). Among participants with diabetes, 45% were been treated (insulin or diabetes pills), and 74% were diagnosed at age  $\geq 40$  (diagnostic criteria for type 2 diabetes/"adult-onset diabetes").

Gender and racial/ethnic distribution significantly differed by diabetes status. Participants with diabetes or prediabetes were older, had lower levels of education, had lower income to poverty ratios, were smokers and obese more often, had more hypertension, arthritis, cardiopathies, stroke and other comorbidities, and presented physical limitations and falls in the past year at a higher proportion than participants who did not have diabetes or prediabetes ( $P < 0.001$ ). Those with prediabetes also had higher total cholesterol levels ( $P < 0.001$ ).

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