Trends in Bone Mineral Density, Osteoporosis, and Osteopenia Among U.S. Adults With Prediabetes, 2005–2014

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Diabetes Care 2020;43:1008–1015 | https://doi.org/10.2337/dc19-1807

OBJECTIVE

We aimed to evaluate trends in bone mineral density (BMD) and the prevalence of osteoporosis/osteopenia in U.S. adults with prediabetes and normal glucose regulation (NGR) and further investigate the association among prediabetes, osteopenia/osteoporosis, and fracture.

RESEARCH DESIGN AND METHODS

We collected and analyzed data from the U.S. National Health and Nutrition Examination Surveys during the period from 2005 to 2014. Femoral neck and lumbar spine BMD data were available for 5,310 adults with prediabetes and 5,162 adults with NGR >40 years old.

RESULTS

A shift was observed toward a lower BMD and a higher prevalence of osteopenia/osteoporosis at the femoral neck and lumbar spine in U.S. adults >40 years old with prediabetes since 2005, especially in men <60 and women ≥60 years old. A shift toward a higher prevalence of osteopenia/osteoporosis at the femoral neck was also observed in adults >40 years old with NGR. Moreover, prediabetes was associated with a higher prevalence of hip fracture, although participants with prediabetes had higher BMD and a lower prevalence of osteopenia/osteoporosis at the femoral neck.

CONCLUSIONS

There was a declining trend in BMD from 2005 to 2014 in U.S. adults >40 years old with prediabetes and NGR, and this trend was more significant in men <60 years old. Populations with prediabetes may be exposed to relatively higher BMD but a higher prevalence of fracture.

Osteoporosis is a common skeletal disease characterized by low bone mass and microarchitectural deterioration of the skeleton, with a consequently increasing rate of bone fragility and predisposition to fracture (1). According to the literature, ~54 million people in the U.S. alone suffer from osteoporosis or low bone mass at the femoral neck and lumbar spine (2). The high prevalence of osteoporosis and the associated fractures poses a major medical burden, emerging as an important public health issue (3).

The prevalence of osteoporosis among older U.S. adults appeared to decline between 1988–1994 and 2005–2006 (4). However, a recent study found that there

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Received 9 September 2019 and accepted 6 February 2020

This article contains Supplementary Data online at https://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-1807/-/DC1.

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was a significant decline in femoral neck bone mineral density (BMD) in the population aged ≥50 years between 2005–2006 and 2013–2014 (5).

The epidemic of glucose metabolism disorders poses another large economic burden, which was estimated to cost nearly $404 billion in the U.S. in 2017 (6). Chronically elevated glucose levels including but not limited to diabetes have deleterious effects on bone, which have been suggested as a complication of inadequately regulated glucose metabolism (7,8). Prediabetes is an intermediate metabolic state between normoglycemia and diabetes, including impaired fasting plasma glucose (FPG), impaired glucose tolerance, and mildly raised hemoglobin A_{1c} (HbA_{1c}). Recent evidence has shown that individuals with prediabetes may have a higher prevalence of diabetes-associated complications than those with normal glucose levels (9).

Based on recent intensive studies, the pathophysiology and clinical management of skeletal fragility in diabetes have been well documented (10,11); however, whether and how prediabetes influences the skeleton remain largely unknown. There have been a few studies on the association between prediabetes and skeletal health showing conflicting results with higher, lower, or similar BMD values compared with those of healthy control subjects (12–14). In particular, little is known about the prevalence and temporal trends of osteopenia and osteoporosis in individuals with prediabetes.

In the current study, we analyzed nationally representative data from the U.S. National Health and Nutrition Examination Survey (NHANES) from 2005 to 2014 to examine the trends of BMD, osteopenia, and osteoporosis in adults with prediabetes and normal glucose regulation (NGR) over a decade and to investigate the association among prediabetes, osteopenia/osteoporosis, and fracture.

RESEARCH DESIGN AND METHODS

Study Design and Study Population

NHANES, conducted by the National Center for Health Statistics, comprise cross-sectional multistage, stratified, clustered probability samples of the U.S. noninstitutionalized population. The study was approved by the National Center for Health Statistics institutional review board, and written informed consent was received from all participants. From 2005 to 2006, the survey started including measurements of the proximal femur and lumbar spine BMD, but BMD was not measured in NHANES in 2011–2012. Hence, only four cycles (2005–2006, 2007–2008, 2009–2010, and 2013–2014) of data were included in the analysis for this study. In the 2013–2014 cycle, DXA scans were only administered to participants aged ≥40 years, and we only included those >40 years old in the main analysis. In total, there were 5,162 subjects with NGR and 5,310 subjects with prediabetes >40 years old who had valid data on BMD or fracture. We also analyzed data on participants aged 20–39 years in NHANES 2005–2010. There were 4,040 subjects with NGR and 1,092 subjects with prediabetes who had valid data on BMD or fracture.

Measurements

The data were collected via household interviews and physical examinations in a mobile examination center. A standardized questionnaire was used to collect information on age, sex, race, education level, milk intake, and history of fracture. Race/ethnicity was self-reported and categorized into Mexican American, other-Hispanic white, other-Hispanic black, and other races. Education was categorized as less than a high school education, high school graduate, and education beyond high school. Milk intake was categorized into five groups: never, rarely (less than once a week), sometimes (once a week or more, but less than once a day), often (once a day or more), and varied. BMI was calculated as weight in kilograms divided by the square of height in meters. Since the 2007–2008 cycle, information on physical activity in the NHANES has been self-reported by participants using the Global Physical Activity Questionnaire. The MET was calculated to estimate average weekly energy expenditure (15).

BMD testing was evaluated by DXA, the examination protocol for which has been described in detail on the NHANES website. The proximal femur and lumbar spine scans in 2005–2006 through 2009–2010 were conducted with a Hologic QDR-4500A fan beam densitometer and with a Hologic Discovery model A densitometer (Hologic, Inc., Bedford, MA) in 2013–2014. The femur scans in 2005–2010 were analyzed with Hologic Discovery v12.4, and the spine scans were analyzed with APEX v3.0. In the 2013–2014 segment, both femur and spine scans were analyzed with APEX v4.0. The Hologic Service Team carried out a cross-calibration procedure to standardize the newer system to the legacy system (16). A previous study assessed five femur regions and confirmed that there was no difference between mean BMD analyzed by Discovery 12.4 and that analyzed by APEX v4.0 at the femoral neck (5).

HbA_{1c} levels were measured in whole blood samples using high-performance liquid chromatography. Although different equipment was used over time, calibration of HbA_{1c} is not necessary according to NHANES recommendations (17). An oral glucose tolerance test was administered using 75 g glucose, followed by venipuncture to measure 2-h plasma glucose (2-h PG). Plasma glucose was measured at the University of Minnesota using a Roche Hitachi 911 instrument in 2005–2006 and a Roche Modular P chemistry analyzer in 2007–2010. In 2013–2014, plasma glucose was measured with a Roche Hitachi cobas C chemistry analyzer at the University of Missouri (Columbia, MO).

In the 2005–2006 survey cycle, a radioimmunoassay (DiaSorin) method was used to measure total 25-hydroxyvitamin D [25(OH)D] (sum of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3). The Centers for Disease Control and Prevention (CDC) changed its vitamin D laboratory method in cycles 2007–2010 to a more analytically accurate assay involving an ultra-high-performance liquid chromatography–tandem mass spectrometric (LC-MS/MS) method. To facilitate comparisons of 25(OH)D across cycles, the CDC standardized concentrations of 25(OH)D measured from radioimmunoassay in previous cycles (including 2005–2006) to predicted LC-MS/MS equivalents using regression equations previously described in detail (18). There were no changes to the laboratory method, laboratory equipment, or laboratory site for this component in the NHANES 2013–2014 cycle. Blood cadmium levels were determined using inductively coupled plasma mass spectrometry in the four survey cycles.

Definition of Variables

Current smoking was defined as having smoked at least 100 cigarettes in one's lifetime and currently smoking cigarettes. Prediabetes was defined as those without

a previous diabetes diagnosis and the satisfaction of at least one of three conditions: *1*) FPG level 5.6–6.9 mmol/L, *2*) HbA_{1c} 5.7–6.4%, or *3*) 2-h PG 7.8–11.0 mmol/L and NGR as FPG <5.6 mmol/L, HbA_{1c} <5.7%, and 2-h PG <7.8 mmol/L. T-scores were calculated as ($BMD_{respondent}$ − mean $BMD_{reference\ group}$)/$SD_{reference\ group}$. Osteopenia was defined as a T-score between −1.0 and −2.5, while osteoporosis was defined as a T-score ≤−2.5. As recommended by the World Health Organization (19), the reference group for calculation of T-scores at the femoral neck consisted of 20–29 non-Hispanic white females from the NHANES III report (20), while the reference group for the lumbar spine was obtained from the Vital and Health Statistics from the CDC (21).

Statistical Analysis

The NHANES uses a complex sampling design that requires the use of sample weights to adjust for the unequal probability of selection into the survey and to adjust for the possible bias resulting from nonresponse, which thus provides estimates representative of the civilian, noninstitutionalized U.S. population. As applied in previous studies (22,23), for the prediabetes and NGR definition, a combination of mobile examination center, FPG, and oral glucose tolerance test weights was used based on the principle of using the smallest subpopulation weight. Eight-year weights were created for 2005–2010 and 2013–2014 estimates by multiplying the 2-year weights by one-fourth. All data analyses were performed using IBM SPSS Statistics, version 24 (IBM Corporation, Armonk, NY). A two-tailed *P* value <0.05 was considered statistically significant.

We used NHANES 2005–2014 to calculate the prevalence of osteopenia, osteoporosis, and fracture in the population stratified by sex and age. The following age categories are recommended by the CDC for reducing the variability in the sample weights and therefore reducing the variance of the estimates: 20–39 years, 40–59 years, and ≥60 years. Tests for trends were calculated by including the midpoint of each survey period as a continuous variable in linear regression models. The relative SE for each estimate was calculated with any relative SE >30% indicating low precision of the estimate (22).

Logistic regression analysis was applied to obtain odds ratios (ORs) of osteopenia/osteoporosis over time with NHANES 2005–2006 as the reference. Model 1 was adjusted for age, sex, race, education level, current smoking status, and BMI. Model 2 was adjusted for model 1 adjustments plus milk intake and 25(OH)D. Model 3 was adjusted for model 2 adjustments plus blood cadmium level; adjustments were made for cadmium because low-level cadmium exposure is known to be associated with decreased BMD and an increased risk of fracture in the general population (24,25). Model 4 was additionally adjusted for physical activity.

Finally, we compared the BMD and prevalence of osteopenia + osteoporosis and fracture between NGR and prediabetes. The association between prediabetes and the odds of osteopenia + osteoporosis and fracture was analyzed by logistic regression. For further evaluation of the bone quality difference between NGR and prediabetes, the prevalence and odds of fracture in subjects with osteopenia/osteoporosis were calculated in the adjusted models as described above.

RESULTS

Characteristics of the Participants Across the Four Survey Cycles

Participants >40 years old with prediabetes in each cycle had comparable age, sex, ethnicity proportions, education level, BMI, and FPG, but those in 2013–2014 had lower levels of 2-h PG and higher HbA_{1c}. Notably, physical activity and blood cadmium levels decreased and 25(OH)D concentrations increased from 2005 to 2014. Generally, participants >40 years old with NGR presented a change trend similar to those in participants with prediabetes, except that they had comparable 2-h PG (Table 1).

Interestingly, BMD of the femoral neck showed a significant decreasing trend in participants >40 years old with prediabetes and NGR through the decade, but BMD of the lumbar spine only showed a decreasing trend in participants >40 years old with prediabetes—not in those with NGR.

Regarding participants aged 20–39 years (Supplementary Table 1), we also observed higher HbA_{1c} levels and lower MET from 2005 to 2010 in both glycemic groups. However, both groups had stable BMD in two bone sites from 2005 to 2010.

Bone Status in Sex-and-Age Stratification Analysis

In men aged 40–59 years with prediabetes, there was a significant decreasing trend for BMD in both sites and, accordingly, an increasing trend for the prevalence of osteopenia + osteoporosis (all P_{trend} <0.05). However, women aged 40–59 years with prediabetes had comparable BMD and prevalence of osteopenia + osteoporosis through the survey cycles. The results in participants >60 years old are quite different. Women >60 years of age with prediabetes had a significantly lower BMD in the femoral neck and a higher prevalence of osteopenia + osteoporosis than the other three survey groups, whereas in corresponding men, these indices were stable throughout the survey cycles (Fig. 1 and Supplementary Table 2).

Among participants >40 years old with NGR, an interesting phenomenon is that men >60 years old had a significant trend of BMD and prevalence of osteopenia + osteoporosis in the lumbar spine (Fig. 1 and Supplementary Table 3).

Finally, in participants aged 20–39 years from 2005 to 2010 (Supplementary Table 4), men with NGR had an elevated trend of osteopenia/osteoporosis prevalence in the femoral neck (P_{trend} = 0.002) and lumbar spine (P_{trend} = 0.04).

Furthermore, we calculated the prevalence of fracture in both sites. Except for the abrupt decline in the lumbar spine in women >60 years old with NGR in 2013–2014, there was no significant trend of fracture prevalence in most of the groups (Supplementary Tables 2–4).

Cycle Trend of Osteopenia and Osteoporosis from 2005 to 2014: Association Analyses

In participants >40 years old, after adjustment for sociodemographics and BMI (model 1), a more recent survey cycle was positively associated with osteopenia + osteoporosis in the lumbar spine for prediabetes (2013–2014 vs. 2005–2006 OR 1.46, 95% CI 1.06–2.02) but not for NGR, and further adjustment for blood cadmium level attenuated its significance. Furthermore, in both prediabetes and NGR, a more recent survey cycle was positively associated with osteopenia/osteoporosis in the femoral neck in the fully adjusted model (model 3, 2013–2014 vs. 2005–2006 OR 1.43, 95% CI 1.01–2.03, and OR 1.40, 95% CI 1.12–1.76, respectively) (Table 2).

Table 1—Characteristics of U.S. adults >40 years old with prediabetes and with NGR, 2005–2014

	NGR					Prediabetes				
	2005–2006	2007–2008	2009–2010	2013–2014	P_{trend}	2005–2006	2007–2008	2009–2010	2013–2014	P_{trend}
N	1,263	1,226	1,335	1,338		927	1,477	1,551	1,355	
Age, years	54.2 ± 0.6	53.2 ± 0.6	53.8 ± 0.3	54.6 ± 0.5	0.42	58.0 ± 0.8	57.8 ± 0.4	58.1 ± 0.4	59.3 ± 0.5	0.08
Women, %	59.2	56.5	58.0	56.4	0.32	46.9	50.4	49.4	52.2	0.15
Race, %					0.41					0.40
Mexican American	4.5	4.8	5.0	4.8		5.1	5.7	6.7	8.1	
Other Hispanic	1.7	3.4	3.3	3.7		2.9	4.3	3.9	4.4	
Non-Hispanic white/ black	81.6/7.6	78.8/7.9	79.2/7.6	77.3/8.1		75.7/11.2	75.5/8.9	73.1/10.6	69.4/10.8	
Other race	4.6	5.1	5.0	6.1		5.0	5.6	5.8	7.3	
Education level, %					0.12					0.12
≤High school	37.1	38.3	36.0	31.0		47.1	46.0	47.2	40.8	
>High school	62.9	61.7	64.0	69.0		52.9	54.0	52.8	59.2	
Current smoker, %	21.6	17.9	14.5	18.5	0.27	23.9	20.3	17.5	19.2	0.13
BMI, kg/m^2	27.3 ± 0.2	27.1 ± 0.2	27.3 ± 0.3	27.6 ± 0.2	0.14	30.5 ± 0.3	28.9 ± 0.2	29.5 ± 0.2	29.9 ± 0.4	0.96
FPG, mmol/L	5.10 ± 0.02	5.15 ± 0.02	5.12 ± 0.02	5.10 ± 0.02	0.81	5.84 ± 0.02	5.86 ± 0.01	5.80 ± 0.02	5.80 ± 0.02	0.07
2-h PG, mmol/L	5.32 ± 0.08	5.22 ± 0.06	5.22 ± 0.05	5.31 ± 0.12	0.94	7.25 ± 0.12	7.14 ± 0.10	7.05 ± 0.09	6.95 ± 0.07	0.02
HbA_{1c}, %	5.22 ± 0.01	5.28 ± 0.01	5.31 ± 0.01	5.28 ± 0.01	<0.001	5.55 ± 0.02	5.63 ± 0.02	5.68 ± 0.01	5.66 ± 0.01	<0.001
HbA_{1c}, mmol/mol	33.6 ± 0.1	34.2 ± 0.1	34.6 ± 0.1	34.2 ± 0.1	<0.001	37.1 ± 0.2	38.0 ± 0.2	38.6 ± 0.2	38.3 ± 0.1	<0.001
MET, min/week[a]	—	3,808 ± 262	2,911 ± 180	2,656 ± 162	0.001	—	3,381 ± 173	3,012 ± 212	2,451 ± 177	<0.001
25(OH)D, nmol/L	63.9 ± 1.1	69.6 ± 1.4	72.4 ± 1.3	74.9 ± 1.7	<0.001	58.8 ± 1.7	68.6 ± 1.1	70.4 ± 1.5	74.9 ± 1.7	<0.001
Blood cadmium, μg/L	0.62 ± 0.06	0.55 ± 0.02	0.50 ± 0.02	0.47 ± 0.05	0.02	0.61 ± 0.04	0.60 ± 0.03	0.55 ± 0.02	0.51 ± 0.04	0.04
Milk intake, %					0.03					0.16
Never/rarely	18.8/13.3	18.8/13.7	17.4/12.8	18.3/17.4		16.2/13.0	18.3/12.9	16.9/14.0	19.5/15.4	
Sometimes/often	23.3/44.0	26.3/40.4	26.9/42.8	27.6/36.5		25.9/44.6	28.0/40.3	26.9/42.0	27.8/36.7	
Varied	0.5	0.7	0	0.3		0.3	0.4	0.2	0.6	
BMD, g/cm^2										
Femoral neck	0.79 ± 0.004	0.80 ± 0.005	0.79 ± 0.004	0.77 ± 0.006	0.03	0.81 ± 0.01	0.81 ± 0.01	0.80 ± 0.005	0.78 ± 0.004	<0.001
Lumbar spine	1.02 ± 0.006	1.02 ± 0.007	1.02 ± 0.008	1.01 ± 0.004	0.36	1.04 ± 0.01	1.02 ± 0.01	1.02 ± 0.01	1.01 ± 0.01	0.03

Data are summarized as the mean ± SE for continuous variables or as a proportion for categorical variables. [a]Consistent MET score calculation was available from 2007 to 2014.

In participants 20–39 years old, for prediabetes and NGR, there was a positive association between survey cycle and osteopenia/osteoporosis in femoral neck (model 3, 2009–2010 vs. 2005–2006 OR 4.52, 95% CI 1.27–16.04, and OR 2.15, 95% CI 1.36–3.40, respectively) (Supplementary Table 5).

Comparison of Bone Status Between Prediabetes and NGR

Participants with prediabetes had significantly greater BMD than those with NGR in both bone sites (Supplementary Table 6). Accordingly, prediabetes seems to be negatively associated with osteopenia/osteoporosis, and this association was significant in the femoral neck in participants >40 years old. However, an interesting finding is that although there was higher BMD in participants with prediabetes, prediabetes was positively associated with hip fracture (Table 3). The association was significant in participants aged 20–39 years (OR 3.77, 95% CI 1.01–14.10) and marginally significant in participants >40 years old (OR 1.57, 95% CI 0.91–2.71) (Table 3).

CONCLUSIONS

In the current study, after adjustment for multiple confounders, including sociodemographic, nutritional, and lifestyle-related risk factors, we found evidence of a shift toward a lower BMD and a higher prevalence of osteopenia/osteoporosis at the femoral neck and lumbar spine in U.S. adults with prediabetes since 2005, especially in men aged <60 and women ≥60 years old. In addition, we also observed a shift toward a higher prevalence of osteopenia/osteoporosis at the femoral neck in U.S. adults with NGR. Interestingly, we found that prediabetes was associated with a higher risk of hip fracture, although these individuals may have higher BMD and a lower prevalence of osteopenia/osteoporosis at the femoral neck. To the best of our knowledge, our study is the first attempt to provide nationally representative estimates of BMD, osteoporosis, and osteopenia in U.S. adults with prediabetes and NGR.

Although the prevalence of osteoporosis in older people declined between 1998–1994 and 2005–2006 (4), concerns have been raised regarding recent downward trends in BMD in the U.S. (5,26). In addition, a recent analysis of the U.S. Medicare database showed that the decreasing trend in hip fracture incidence appeared to have ended in 2013–2015 (27). Our study further confirms this trend of osteoporosis/osteopenia in participants with prediabetes and NGR. This is a concern given the substantial growth of this population over the past 25 years, which was up to 36.2% of U.S. adults (28). In contrast, we did not observe an increasing trend in hip or spine fracture in the present analysis. It is worth mentioning that the prevalence of fracture was small in each subgroup, which may bias the study results.

To identify possible reasons behind the observed osteopenia/osteoporosis trends, we examined changes in sociodemographic variables (age, sex, race, and education level) and nutritional [25(OH)D, milk intake], environmental (cadmium), and lifestyle-related risk factors (BMI, smoking, and physical activity) between survey periods. Adjustment for sociodemographic, BMI, and nutritional variables

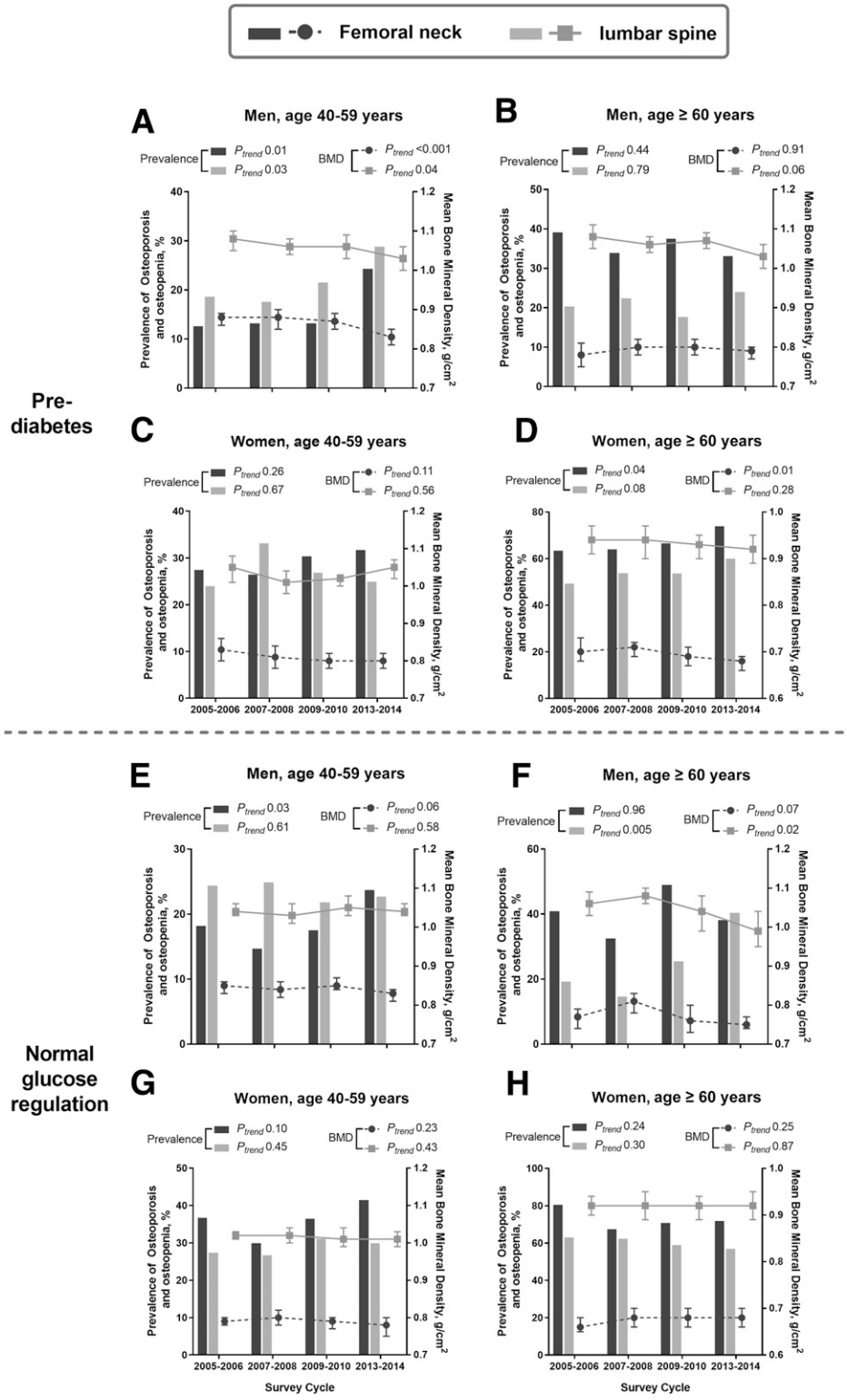

Figure 1—BMD and prevalence of osteopenia + osteoporosis in the femoral neck and lumbar spine for participants with prediabetes and NGR by age and sex from 2005–2006 to 2013–2014. Data on BMD are expressed as mean and 95% CI.

did not markedly alter conclusions regarding trends, indicating that these factors may not play a major role in the observed changes in skeletal status. Although blood cadmium levels have been decreasing in the U.S. population, adjustment for cadmium slightly alters conclusions regarding femoral neck BMD trends in participants with prediabetes and NGR and renders the trends of lumbar spine BMD in participants with prediabetes nonsignificant. It is well established that low-level cadmium exposure is associated with an increased risk of low bone mass (24,25), and there may be no safe

Table 2—Trends in osteopenia + osteoporosis in participants >40 years old with prediabetes and NGR

	2005–2006	2007–2008	2009–2010	2013–2014	P_{trend}
Prediabetes					
Femoral neck					
Prevalence (%)	31.0	31.5	34.0	40.0	
Model 1	1.00 (Ref.)	0.85 (0.62–1.16)	1.04 (0.75–1.44)	1.42 (1.08–1.88)	0.001
Model 2	1.00 (Ref.)	0.90 (0.65–1.25)	1.14 (0.82–1.57)	1.60 (1.18–2.16)	<0.001
Model 3	1.00 (Ref.)	0.89 (0.64–1.24)	1.13 (0.82–1.55)	1.43 (1.01–2.03)	0.02
Model 4	—	1.00 (Ref.)	1.24 (0.89–1.72)	1.56 (1.10–2.22)	0.02
Lumbar spine					
Prevalence (%)	25.6	30.2	28.5	33.1	
Model 1	1.00 (Ref.)	1.14 (0.80–1.63)	1.11 (0.84–1.45)	1.46 (1.06–2.02)	0.04
Model 2	1.00 (Ref.)	1.19 (0.83–1.70)	1.14 (0.86–1.52)	1.53 (1.08–2.17)	0.03
Model 3	1.00 (Ref.)	1.19 (0.83–1.70)	1.12 (0.82–1.52)	1.35 (0.97–1.87)	0.14
Model 4	—	1.00 (Ref.)	0.92 (0.64–1.33)	1.13 (0.77–1.65)	0.57
NGR					
Femoral neck					
Prevalence (%)	38.1	30.2	36.6	40.5	
Model 1	1.00 (Ref.)	0.71 (0.53–0.95)	1.03 (0.81–1.31)	1.27 (1.00–1.61)	0.003
Model 2	1.00 (Ref.)	0.75 (0.53–1.05)	1.07 (0.84–1.38)	1.34 (1.05–1.72)	0.002
Model 3	1.00 (Ref.)	0.75 (0.53–1.06)	1.08 (0.84–1.40)	1.40 (1.12–1.76)	0.001
Model 4	—	1.00 (Ref.)	1.44 (1.04–2.00)	1.86 (1.36–2.55)	<0.001
Lumbar spine					
Prevalence (%)	30.8	29.3	30.5	31.5	
Model 1	1.00 (Ref.)	0.96 (0.68–1.34)	1.05 (0.75–1.47)	1.12 (0.86–1.45)	0.30
Model 2	1.00 (Ref.)	1.01 (0.71–1.44)	1.10 (0.79–1.54)	1.20 (0.91–1.57)	0.14
Model 3	1.00 (Ref.)	1.02 (0.72–1.44)	1.09 (0.78–1.52)	1.21 (0.85–1.72)	0.27
Model 4	—	1.00 (Ref.)	1.07 (0.74–1.54)	1.15 (0.78–1.70)	0.49

Data are summarized as OR (95% CI) unless otherwise indicated. Model 1 was adjusted for age, sex, race, education level, current smoking status, and BMI. Model 2 was adjusted for model 1 adjustments plus milk intake and 25(OH)D. Model 3 was adjusted for model 2 adjustments plus blood cadmium level. Model 4 was additionally adjusted for physical activity (MET score), which was available from 2007 to 2014. Ref., reference.

threshold for blood cadmium. Future efforts may still be needed to further reduce cadmium pollution. Additional studies are also needed to explain the association between blood cadmium and the recent BMD decline in the U.S. population with prediabetes and NGR.

Notably, we found the BMD loss in men younger than 60 years old is particularly severe in the femoral neck, which has fallen to almost the same level as that of women in 2013–2014. Since BMD at the femoral neck has the highest predictive value for hip fracture and since the hip is the site of highest clinical relevance (29), this finding has clinical importance. At present, most people and even some clinicians still believe that osteoporosis is a disorder only of concern for the elderly adults, especially postmenopausal women. There are far fewer and less powered studies on osteoporosis in men than in women. Osteoporosis in men remains largely underdiagnosed and undertreated (30). Our findings should raise awareness that BMD in younger males is declining. Educational programs are warranted for these vulnerable younger men with prediabetes to help prevent falls in later life.

Recently, there has been growing appreciation of the link between diabetes and skeletal health. It is well acknowledged that both type 1 and type 2 diabetes predispose subjects to a higher risk of fractures, although type 1 diabetes is characterized by lower BMD, whereas type 2 diabetes is associated with an average or even high BMD (31). Nevertheless, few studies have explored the association between prediabetes and skeletal health, and studies show conflicting results with higher, lower, or similar BMD values compared with those found in healthy control subjects (12–14). In the present analysis, we found that compared with subjects with NGR, those with prediabetes have a lower prevalence of osteopenia/osteoporosis but a higher prevalence of fractures. Thus, similar to in type 2 diabetes and BMD, the bone in prediabetes appears to also have reduced strength for a given BMD, and as a result, the standard tools (BMD) appear to underestimate fracture risk in individuals with prediabetes, posing a challenge for clinicians.

With the high prevalence of prediabetes taken into account, successive intervention in this large population can have important implications for public health. It is already known that for people with prediabetes, a physically active and healthy lifestyle could reduce both the risk of further progression to diabetes (32) and the incidence of mortality due to cardiovascular and all other causes (33). Interestingly, Skoradal et al. (34) recently reported that recreational football training provided a powerful osteogenic stimulus and improved bone health in 55- to 70-year-old sedentary men and women with prediabetes. This study is important and sheds light on the equally beneficial effect of lifestyle interventions on skeletal health in patients suffering from prediabetes. In addition, optimum calcium and vitamin D repletion represent the mainstay of prevention for osteoporosis in patients with prediabetes. Larsen et al. (35) found that vitamin D supplementation had a positive effect on BMD in males with prediabetes. However, there is currently no evidence that bisphosphonates are useful in preventing osteoporosis in individuals with prediabetes, and possible side effects such as osteonecrosis of the jaw and esophageal cancer should be considered when initiating bisphosphonates (36). Further studies are warranted to determine which phenotype of prediabetes can benefit from active pharmacological treatment.

A key strength of this analysis is the source of the data. NHANES is a series of meticulously conducted surveys with continuous quality control, ensuring that the data are timely and of high quality. NHANES also uses population-based cluster random selection to identify a nationally representative sample that can be applied to the whole U.S. population. However, it has some limitations: First, the major limitation is that NHANES is performed as an independent "snapshot." Data could only explore secular trends but failed to provide longitudinal follow-up data. Second, all of the participants recruited in NHANES were noninstitutionalized. Since institutionalized individuals tend to have lower bone mass (37), we may have underestimated the actual prevalence in the total population. However, this limitation is unlikely to have altered

Table 3—Association between prediabetes and odds of osteopenia + osteoporosis and fracture

	Age 20–39 years			Age ≥40 years		
	NGR	Prediabetes	*P*	NGR	Prediabetes	*P*
Femoral neck						
Prevalence (%)	11.6	4.7		36.7	34.2	
Model 1	1.00 (Ref.)	0.59 (0.42–0.84)	0.005	1.00 (Ref.)	0.85 (0.73–0.99)	0.037
Model 3	1.00 (Ref.)	0.54 (0.37–0.79)	0.002	1.00 (Ref.)	0.85 (0.73–1.00)	0.046
Model 2	1.00 (Ref.)	0.54 (0.37–0.79)	0.002	1.00 (Ref.)	0.85 (0.72–1.00)	0.046
Model 4	1.00 (Ref.)	0.51 (0.33–0.77)	0.002	1.00 (Ref.)	0.85 (0.70–1.04)	0.12
Lumbar spine						
Prevalence (%)	16.8	13.9		30.6	29.3	
Model 1	1.00 (Ref.)	0.97 (0.69–1.35)	0.85	1.00 (Ref.)	0.96 (0.81–1.13)	0.59
Model 3	1.00 (Ref.)	1.01 (0.71–1.43)	0.96	1.00 (Ref.)	0.97 (0.82–1.13)	0.66
Model 2	1.00 (Ref.)	1.00 (0.70–1.42)	1.00	1.00 (Ref.)	0.92 (0.77–1.10)	0.35
Model 4	1.00 (Ref.)	1.12 (0.75–1.67)	0.59	1.00 (Ref.)	0.92 (0.72–1.16)	0.45
Hip fracture						
Prevalence (%)	0.5	0.7		1.4	2.0	
Model 1	1.00 (Ref.)	1.92 (0.68–5.44)	0.22	1.00 (Ref.)	1.28 (0.77–2.11)	0.34
Model 2	1.00 (Ref.)	2.31 (0.76–7.05)	0.14	1.00 (Ref.)	1.21 (0.74–1.96)	0.44
Model 3	1.00 (Ref.)	2.40 (0.80–7.16)	0.12	1.00 (Ref.)	1.57 (0.97–2.53)	0.07
Model 4	1.00 (Ref.)	3.77 (1.01–14.10)	0.048	1.00 (Ref.)	1.57 (0.91–2.71)	0.11
Spine fracture						
Prevalence (%)	1.7	1.5		2.8	2.8	
Model 1	1.00 (Ref.)	0.94 (0.38–2.31)	0.89	1.00 (Ref.)	0.88 (0.58–1.33)	0.53
Model 2	1.00 (Ref.)	1.01 (0.40–2.56)	0.98	1.00 (Ref.)	0.91 (0.59–1.39)	0.66
Model 3	1.00 (Ref.)	1.04 (0.41–2.63)	0.94	1.00 (Ref.)	0.96 (0.60–1.55)	0.88
Model 4	1.00 (Ref.)	1.33 (0.48–3.72)	0.58	1.00 (Ref.)	1.47 (0.82–2.63)	0.19

Data are summarized as OR (95% CI) unless otherwise indicated. Model 1 was adjusted for age, sex, race, education level, current smoking status, and BMI. Model 2 was adjusted for model 1 adjustments plus milk intake and 25(OH)D. Model 3 was adjusted for model 2 adjustments plus blood cadmium level. Model 4 was additionally adjusted for physical activity. Ref., reference.

the observed trends given that the institutionalized population only constitutes a small proportion of the entire U.S. population. Third, although we have examined changes in sociodemographic, nutritional, environmental, and lifestyle-related risk factors among survey periods, other potential residual confounders, such as mental stress and other environmental endocrine-disrupting chemicals, may still exist. Further studies are warranted to explain the observed BMD decline.

In conclusion, our findings serve as an alert of the declining trend of BMD and the increasing trend in the prevalence of osteopenia and osteoporosis among U.S. adults with prediabetes and NGR. Guidelines for the treatment of diabetes are increasingly comprehensive, and therefore, the incidence of complications has significantly declined in the past two decades (38). However, the lack of research and accepted guidelines for prediabetes has made the prevalence of diabetes-related complications virtually the same for people with prediabetes compared with people with diabetes (39). More importantly, data for the optimum management of osteoporosis in prediabetes are scarce. More research is needed to fully investigate the progression of bone changes from normoglycemia to prediabetes and consider possible therapeutic interventions to mitigate skeletal fragility in this ever-growing population.

Acknowledgments. The authors express gratitude to Jihui Zhang, the Chinese University of Hong Kong, for helping with the weighting methodology in the revised manuscript.

Funding. This study was supported by the Science and Technology Commission of Shanghai Municipality (19140902400), National Natural Science Foundation of China (81870559, 81561128014), and the Municipal Human Resources Development Program for Outstanding Young Talents in Medical and Health Sciences in Shanghai (2017YQ053).

The funders played no role in the design or conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. N.W. wrote the manuscript, researched data, and reviewed and edited the manuscript. P.X. reviewed and edited the manuscript. C.C. and Q.C. wrote the manuscript, researched data, and contributed to the discussion. B.N. reviewed and edited the manuscript and contributed to the discussion. H. Zhang, H. Zhai, and L.Z. researched data. Y.L. contributed to the discussion. N.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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