Original Article

National trends in insulin resistance and β-cell dysfunction among adults with prediabetes: NHANES 2001−2016

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Abstract

Background: Insulin resistance is the central abnormality and mechanism underlying the progression of cardiometabolic-based chronic diseases. This study aimed to evaluate the trends in insulin resistance and β-cell dysfunction from 2001 to 2016 among US adults with undiagnosed diabetes, prediabetes, and normal glucose regulation and to provide sex-specific information using data from National Health and Nutrition Examination Surveys (NHANES) 2001−2016.

Methods: Data from 14,481 participants aged over 20 years from 8 consecutive 2-year cross−sectional cycles of the NHANES from 2001 to 2016 were used. Updated homoeostasis model assessment 2 (HOMA2: HOMA2%B for β-cell function and HOMA2IR for insulin resistance) was used as a surrogate measure. We defined the upper sex-specific tertile of HOMA2IR as insulin resistance and the lower corresponding tertile of HOMA2%B as low β-cell function.

Results: In both sexes with undiagnosed diabetes, HOMA2%B (men, $P_{trend} = 0.118$; women, $P_{trend} = 0.184$) and HOMA2IR (men, $P_{trend} = 0.710$; women, $P_{trend} = 0.855$) remained stable over time. In the prediabetes group, both sexes exhibited significant increasing trends in HOMA2%B (men, $P_{trend} < 0.010$; women, $P_{trend} < 0.010$) and HOMA2IR (men, $P_{trend} < 0.010$; women, $P_{trend} < 0.050$). Adjusting for waist circumference mildly attenuated the trend in HOMA2IR and insulin resistance in men ($P_{trend} < 0.010$), but it resulted in no significance in women ($P_{trend} = 0.196$). In regard to normal glucose regulation, both sexes presented significant decreasing trends in low β-cell function (men, $P_{trend} < 0.050$; women < 0.010) and attenuated trends in insulin resistance (men, $P_{trend} = 0.196$; women, $P_{trend} = 0.121$).

Conclusions: Over 16 years, insulin resistance demonstrated an increasing trend in adult US population with prediabetes, while β-cell function showed a compensatory increasing trend. Identifying people with prediabetes early and focusing on reducing insulin resistance as the intervention core, especially controlling central obesity, might increase the opportunity for cardiovascular and diabetes risk reduction.

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Introduction

The epidemic of glucose metabolism disorders has become a serious global health care burden, resulting in adverse effects on mortality, morbidity and healthcare expenditure.[1,2] In the overall US population, the prevalence of diabetes has increased rapidly from 7.7% in 1999−2000 to 13.3% in 2015−2016.[3] Prediabetes is considered a heterogeneous subclinical status of diabetes. Its prevalence increased substantially over the past two decades and reached up to 36.2% of US adults.[4] The population with prediabetes has a higher risk of developing diabetes, and in individuals aged 45 years, the lifetime conversion rate to diabetes is as high as 74%.[5] To make matters worse, cardiovascular and renal risks precede diabetes and are evident in people with prediabetes.[6] Considering the millions of people with prediabetes across the US, the impact on cardiovascular and renal health is staggering. Hence, it is of public health priority to identify and effectively prevent or delay the progression and consequences of prediabetes early.

Commonly, insulin resistance and β-cell dysfunction are considered the two critical pathological bases for the development of glucose metabolism disorders, while insulin resistance also plays a core mediating role in other conditions from adiposity and metabolic syndrome to cardiovascular diseases, making insulin resistance in the context of prediabetes a serious problem.[7] Accumulating evidence has shown that insulin resistance and impaired β-cell function already coexist in individuals with prediabetes.[8] Several studies have indicated that the fast development of insulin resistance over time inducing the failure of a compensatory increase in insulin secretion is the driving cause of the conversion from normal glucose regulation (NGR) to prediabetes and from prediabetes to type 2 diabetes,[9,10] while others consider the ever-deteriorating β-cell function over time as the primary pathology.[11,12]

However, little is known about the recent trends in insulin resistance and β-cell function in populations with different glycemic statuses in the 21st century, which is of critical importance to provide evidence for future implementation of national health policies and priorities from the pathophysiological level in the corresponding population. To address these unanswered questions, we analyzed nationally representative data from National Health and Nutrition Examination Surveys (NHANES) from 2001 to 2016 to examine insulin resistance and β-cell function in men and women over time.

Methods

Study design and study population

The NHANES, conducted by the National Center for Health Statistics (NCHS), is conducted with cross-sectional, multistage, stratified, clustered probability samples of the U.S. noninstitutionalized population. The NHANES was approved by the NCHS institutional review board, and written informed consent was received from all participants. The Ethics Committee of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine determined that the current study was exempt from review and informed consent given the use of publicly available data.

Data from 8 consecutive 2-year cycles of NHANES from 2001 to 2002 and 2015 to 2016 were used. We included adults aged over 20 years with fasting plasma glucose (FPG) and insulin data (20−400 pmol/L). The exclusion criteria were pregnancy and diagnosed diabetes. Finally, 14,481 participants were included.

Measurements

The data were collected via household interviews and physical examinations in a mobile examination center. A standardized questionnaire was used to collect demographic information and medical history. Race/ethnicity was self-reported and categorized into Mexican American, non-Hispanic white, non-Hispanic black, and other races. Education was categorized as less than a high school education and education beyond high school. Current smoking was defined as having smoked at least 100 cigarettes in one's lifetime and currently smoking cigarettes. The poverty-income ratio was used to categorize income (above vs at or below the poverty level).[6]

After resting quietly in a seated position for 5 minutes and once the participants' maximum inflation level has been determined, three consecutive blood pressure readings were obtained. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2) and categorized into normal (BMI <25 kg/m^2), overweight (BMI 25−29 kg/m^2)

and obese (BMI ≥ 30 kg/m^2). Waist circumference (WC) was also measured.

Glycosylated Hemoglobin (HbA1c) levels were measured in whole blood samples using high-performance liquid chromatography. Although different equipment was used throughout the study period, calibration of HbA1c was not necessary according to NHANES recommendations.[13] FPG was measured. In the 2005−2016 NHANES, an oral glucose tolerance test was administered using 75 g of glucose, followed by venipuncture to measure 2-hour plasma glucose (2-hour PG). To assess the trend in FPG, 2-hour PG and plasma insulin within the 8 consecutive NHANES cycles, we calibrated the values according to the equations provided by the NCHS as performed in previous studies.[14]

Definition of variables

Undiagnosed diabetes was defined as any participant without a previous diabetes diagnosis who had a hemoglobin A1c level of 6.5% or greater, an FPG level of 7.0 mmol/L or greater, or a 2-hour PG level of 11.1 mmol/L or greater. Prediabetes was defined as those without a previous diabetes diagnosis who satisfied at least one of the following three conditions: (i) FPG level of 5.6−6.9 mmol/L; (ii) HbA1c of 5.7%−6.4%; or (iii) 2-hour PG of 7.8−11.0 mmol/L. NGR was defined as those without a previous diabetes diagnosis with an FPG less than 5.6 mmol/L, HbA1c less than 5.7% and a 2-hour PG less than 7.8 mmol/L.[15]

Given the large sample size, it was not feasible to perform sophisticated measures of insulin resistance and impaired β-cell function; hence, homoeostasis model assessment (HOMA) was used as a surrogate measure. An updated HOMA2 model was used, which simulates the physiological processes that influence circulating glucose and insulin levels to derive estimates of β-cell function (HOMA2%B) and insulin resistance (HOMA2IR).[16] "The HOMA2 model is a structural computer model of the glucose-insulin feedback system in the homeostatic (overnight-fasted) state. The model consists of a number of nonlinear empirical equations describing the functions of organs and tissues involved in glucose regulation".[16] In participants without undiagnosed diabetes, sex-specifically, we defined the upper tertile of HOMA2IR as indicative of insulin resistance, the mid tertile as indicative of intermediate condition, and the lower tertile as indicative of no insulin resistance. Similarly, for β-cell function, the lower tertile was defined as

low β-cell function, the mid tertile as intermediate β-cell function, and the upper tertile as high β-cell function.[10] The cutoff values were also applied for individuals with undiagnosed diabetes.

Statistical analysis

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 US population. As described in previous studies,[14,17] for undiagnosed diabetes, prediabetes and NGR definitions, 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. Missing data ranged from 1.4% (BMI) to 3.7% (waist circumference) and were lower than 10%; thus, they were not imputed according to the NHANES analytical guide. All data analyses were performed using IBM SPSS Statistics, Version 24 (IBM Corporation, Armonk, NY, USA) by the Complex Samples module. A two-tailed P value < 0.05 was considered statistically significant.

To increase the sample size in each analytic period, we combined every two survey cycles into one period (2001−2004, 2005−2008, 2009−2012 and 2013−2016). For each glycemic group (undiagnosed diabetes, prediabetes, and normal glycemia) in each period, we reported sociodemographic and clinical characteristics. Using multiple logistic and linear regression, we tested for trends in distributional differences in these characteristics in successive periods. Tests for trends were performed by including the midpoint of each survey period as a continuous variable in a regression model.

Among men and women with undiagnosed diabetes, prediabetes and NGR, HOMA2%B and HOMA2IR were estimated in each period and are presented as the mean (standard error). Trend results are also given. P_{trend1} was unadjusted. P_{trend2} was from the model adjusted for age, current smoking, education, poverty status, and body mass index. P_{trend3} was from the model adjusted for age, current smoking, education, poverty status, and waist circumference. Then, in men and women, we assessed the proportions of individuals with and without insulin resistance and individuals with low and high β-cell function.

Then, we analyzed the sex-specific association of insulin resistance and low β-cell function with each 2-survey-cycle increments in the undiagnosed diabetes,

prediabetes, and normal glycemia groups. Model 1 was unadjusted. Model 2 was adjusted for age, race, current smoking, education, at or below poverty line. Model 3 was adjusted for age, race, current smoking, education, at or below poverty line, and waist circumference.

Finally, we also combined insulin resistance and β-cell function categories. Trends in insulin resistance plus low β-cell function, and insulin resistance plus high β-cell function, the two important conditions, are reported.

Results

Characteristics of participants

We obtained data for 14,481 eligible individuals: 3234 from the survey period 2001−2004, 3309 from 2005 to 2008, 4031 from 2009 to 2012, and 3907 from 2013 to 2016. Among the three glycemic groups, the mean age and sex distributions remained largely stable from 2001 to 2004 to 2013−2016 (Table 1). Over

Table 1
Characteristics of US adults aged ≥20 years by glycemic status and survey cycles according to the data from NHANES 2001 to 2016.

Characteristics	2001−2004	2005−2008	2009−2012	2013−2016	P_{trend}
Undiagnosed diabetes	$n = 186$	$n = 345$	$n = 412$	$n = 328$	
Age (years)	58.9 (1.7)	61.8 (1.1)	59.2 (0.9)	59.1 (0.9)	0.283
Male (%)	64.8 (4.7)	52.2 (3.3)	47.0 (3.6)	49.4 (4.7)	0.068
Completed high-school and lower (%)	50.8 (6.0)	61.4 (4.7)	52.2 (3.2)	44.3 (4.4)	0.051
Current smoker (%)	18.4 (3.4)	19.2 (2.9)	16.3 (2.6)	19.0 (2.3)	0.909
Race (%)					
Mexican American	6.9 (2.2)	8.8 (1.8)	11.6 (2.5)	9.8 (2.2)	0.307
Non-Hispanic white	72.0 (5.1)	75.0 (3.4)	65.9 (4.1)	66.7 (4.7)	0.061
Non-Hispanic black	10.5 (2.1)	10.8 (1.8)	9.1 (2.1)	9.5 (2.2)	0.067
Other Races	10.6 (4.0)	5.4 (1.7)	13.4 (2.2)	14.0 (2.7)	−
BMI (kg/m²)	31.9 (0.9)	31.8 (0.5)	32.0 (0.4)	31.8 (0.5)	0.963
Waist circumference (cm)	109.6 (1.9)	108.8 (1.1)	108.1 (0.8)	108.5 (1.6)	0.664
At or below poverty line (%)	10.3 (1.6)	10.6 (1.9)	16.6 (2.8)	17.9 (2.6)	<0.010
Prediabetes	$n = 1477$	$n = 1715$	$n = 1920$	$n = 1926$	
Age (years)	49.9 (0.7)	49.4 (0.6)	50.8 (0.6)	50.9 (0.5)	0.069
Male (%)	59.1 (1.3)	55.4 (1.3)	55.3 (1.4)	54.2 (1.5)	<0.050
Completed high-school and lower (%)	47.4 (2.0)	46.0 (2.2)	43.0 (2.0)	39.1 (2.6)	<0.010
Current smoker (%)	21.7 (1.7)	21.3 (1.4)	19.7 (1.2)	18.6 (1.6)	0.118
Race (%)					
Mexican American	7.8 (1.7)	9.2 (1.4)	8.1 (1.3)	10.4 (1.7)	0.337
Non-Hispanic white	74.4 (3.0)	70.6 (2.7)	69.2 (2.4)	65.1 (2.5)	<0.010
Non-Hispanic black	8.3(1.1)	9.9 (1.4)	10.5 (1.1)	9.2 (1.2)	<0.050
Other Races	9.5 (1.6)	10.4 (1.4)	12.2 (1.2)	15.4 (1.3)	
BMI (kg/m²)	29.5 (0.2)	30.3(0.2)	30.0 (0.2)	30.6 (0.2)	<0.050
Waist circumference (cm)	101.3 (0.6)	102.5 (0.5)	102.7 (0.4)	103.9 (0.6)	<0.010
At or below poverty line (%)	10.7 (1.3)	11.5 (1.2)	13.1 (1.0)	14.8 (1.1)	<0.050
Normal glucose regulation	$n = 1571$	$n = 1249$	$n = 1699$	$n = 1653$	
Age (years)	40.6 (0.6)	38.9 (0.5)	40.1 (0.7)	40.6 (0.6)	0.571
Male (%)	42.0 (1.4)	42.9 (1.5)	43.4 (1.2)	43.0 (1.5)	0.617
Completed high-school and lower (%)	40.7 (1.5)	37.0 (2.0)	31.3 (2.2)	32.0 (2.7)	<0.010
Current smoker (%)	25.9 (1.7)	21.8 (1.3)	17.1 (1.3)	19.6 (1.8)	<0.010
Race(%)					
Mexican American	8.0 (1.4)	8.7 (0.9)	8.5 (1.5)	7.6 (1.2)	<0.050
Non-Hispanic white	71.8 (2.9)	68.8 (2.2)	68.5 (2.4)	66.6 (2.9)	<0.010
Non-Hispanic black	11.8 (1.7)	11.5 (1.6)	9.7 (1.0)	10.9 (1.7)	<0.010
Other Races	8.4 (1.4)	11.1(1.6)	13.3 (1.5)	14.9 (1.3)	
BMI (kg/m²)	27.7 (0.2)	27.7 (0.2)	27.4 (0.3)	28.0 (0.2)	0.487
Waist circumference (cm)	94.8 (0.4)	94.5 (0.6)	94.1 (0.7)	95.7 (0.6)	0.242
At or below poverty line (%)	13.3 (1.3)	10.9 (1.1)	14.3 (1.2)	14.7 (1.9)	0.272

All estimates include standard errors in parentheses. Undiagnosed diabetes was defined as no self-reported diabetes diagnosis and FPG ≥126 mg/dL (7.0 mmol/L) or HbAlc ≥6.5% (48 mmol/mol) or Oral Glucose Tolerance Test ≥ 200 mg/dL. Characteristics of prediabetes population was for the group defined as no-self reported diabetes and FPG 100−125 mg/dL (5.6−6.9 mmol/L) or HbA1c 5.7%−6.4% (39−47 mmol/mol) or Oral Glucose Tolerance Test 140−199 mg/dL. Normal glycemic status was defined by no reported diabetes diagnosis and FPG <100 mg/dL (5.6 mmol/L) and HbA1c <5.7% (39 mmol/mol) or Oral Glucose Tolerance Test <140 mg/dL. NHANES: National Health and Nutrition Examination Survey; BMI: Body mass index.

time, although more people had better education, larger proportions of people with undiagnosed diabetes and prediabetes were living in poverty. Among the prediabetes group, the proportions of non-Hispanic white participants showed decreasing trends over time. It is noteworthy that both BMI and WC significantly increased only in the prediabetes group over time.

In Supplemental Table 1, from NGR to prediabetes to undiagnosed diabetes, people were more prone to being older, having lower education, and having greater BMI and WC (all P_{trend} <0.01). With worse glucose regulation, participants also had lower HOMA2%B and higher HOMA2IR and correspondingly had a greater prevalence of low β-cell function and insulin resistance.

Supplemental Table 2 shows the associations among HOMA2%B and HOMA2IR (dependent variables) and the main variables (independent variables). Higher HOMA2%B was significantly associated with younger age, and higher WC, male sex, Mexican American race, living at or below the poverty line and NGR. Furthermore, greater HOMA2IR was significantly associated with younger age, and higher WC, female

sex, Mexican American race, higher education, undiagnosed diabetes, and prediabetes status.

HOMA2%B and HOMA2IR trends by sex

We divided the US adults by sex and glycemic status (Table 2). In men and women with undiagnosed diabetes, the trends in HOMA2%B and HOMA2IR remained stable over time regardless of whether the unadjusted or adjusted model was used. In the prediabetes group, however, both sexes had increasing trends of HOMA2%B and HOMA2IR in the unadjusted model, and adjusting for age, race, current smoking, education, poverty status, and BMI (model 2) or WC (model 3) did not alter the significant trend of HOMA2%B. Adjusting for weight indices mildly attenuated the trend in HOMA2IR in men, but in women, P_{trend} changed from 0.022 to 0.096 after adjusting for demographic parameters and BMI and to 0.196 after adjusting for demographic parameters and WC. In the NGR group, men and women also showed differences. In men, no significant trends in HOMA2%B or HOMA2IR were present. In women, significant increasing trends in HOMA2%B and HOMA2IR were

Table 2

HOMA2B and HOMA2IR in US adults aged 20 years and older, by sex and glycemic status, 2001−2016.

Items	2001−2004	2005−2008	2009−2012	2013−2016	P_{trend1}	P_{trend2}	P_{trend3}
Men							
Undiagnosed diabetes	$n = 104$	$n = 194$	$n = 214$	$n = 177$			
HOMA2B (%)	67.8 (57.3, 78.3)	80.1 (74.1, 86.0)	87.7 (80.9, 94.5)	80.8 (72.7, 88.9)	0.118	0.067	0.081
HOMA2IR	2.85 (2.24, 3.46)	2.32 (2.09, 2.54)	2.90 (2.60, 3.20)	2.64 (2.24, 3.04)	0.710	0.399	0.527
Prediabetes	$n = 851$	$n = 953$	$n = 1046$	$n = 1001$			
HOMA2B (%)	85.9 (82.2, 89.7)	96.0 (92.5, 99.4)	104.3 (100.1, 108.5)	99.0 (95.2, 102.8)	<0.010	<0.010	<0.010
HOMA2IR	1.52 (1.43, 1.62)	1.74 (1.65, 1.84)	1.90 (1.78, 2.02)	1.80 (1.69, 1.91)	<0.010	<0.010	<0.010
NGR	$n = 685$	$n = 549$	$n = 686$	$n = 683$			
HOMA2B (%)	99.4 (95.3, 103.5)	99.9 (96.3, 103.4)	106.3 (101.4, 111.2)	101.2 (96.2, 106.2)	0.188	0.212	<0.05
HOMA2IR	1.24 (1.16, 1.31)	1.23 (1.16, 1.30)	1.33 (1.24, 1.41)	1.23 (1.13, 1.34)	0.733	0.914	0.438
Women							
Undiagnosed diabetes	$n = 82$	$n = 151$	$n = 198$	$n = 151$			
HOMA2B (%)	68.7 (59.9, 77.5)	87.1 (80.3, 93.8)	90.1 (83.8, 96.4)	87.0 (76.4, 97.6)	0.184	0.284	0.107
HOMA2IR	2.48 (2.07, 2.90)	2.47 (2.20, 2.74)	2.37 (2.08, 2.65)	2.38 (2.05, 2.71)	0.855	0.422	0.987
Prediabetes	$n = 626$	$n = 762$	$n = 874$	$n = 925$			
HOMA2B (%)	95.6 (92.0, 99.2)	98.4 (94.3, 102.5)	106.7 (103.0, 110.5)	104.9 (100.7, 109.1)	<0.010	<0.010	<0.010
HOMA2IR	1.74 (1.63, 1.85)	1.67 (1.57, 1.76)	1.83 (1.75, 1.92)	1.83 (1.73, 1.94)	<0.050	0.096	0.196
NGR	$n = 886$	$n = 700$	$n = 1013$	$n = 970$			
HOMA2B (%)	96.7 (92.9, 100.4)	98.8 (94.4, 103.1)	103.0 (99.6, 106.5)	103.9 (99.8, 108.0)	<0.010	<0.010	<0.010
HOMA2IR	1.10 (1.03, 1.17)	1.15 (1.06, 1.24)	1.16 (1.10, 1.22)	1.19 (1.12, 1.26)	<0.010	<0.050	0.121

Data are shown as mean (95% confidence interval). P_{trend1} was from model unadjusted. P_{trend2} was from model adjusted for age, race, current smoking, education, at or below poverty line, and body mass index. P_{trend3} was from model adjusted for age, race, current smoking, education, poverty status, and waist circumference. Linear regression was used by including the midpoint of each survey period as a continuous variable. HOMA2B and HOMA2IR were natural-log transformed when calculating P_{trend}. HOMA2%B: homoeostasis model assessment 2 for β-cell function; HOMA2IR: homoeostasis model assessment 2 for insulin resistance.

observed, and the significant trend in HOMA2IR was completely mitigated by WC but not BMI.

Association between insulin resistance and β-cell dysfunction in the study periods

In men and women with prediabetes from 2001 to 2016, the prevalence of low β-cell function decreased from 44.5% to 42.4%−31.7% and 33.1%, while the prevalence of insulin resistance increased from 29.8% to 39.6%−39.2% and 45.5%, respectively (Fig. 1, Supplemental Table 3). In the regression analyses, in the prediabetes group, every two-survey-cycle increment was significantly associated with insulin resistance (men: odds ratios [OR] 1.15; 95% confidence interval [CI] 1.05, 1.26; women: OR 1.14, 95% CI 1.04, 1.25) in the adjusted model. After further adjusting for WC, the significance disappeared in women. The inverse association of the two-survey-cycle increments with low β-cell function was

significant in individuals with prediabetes and NGR (Table 3).

Trends in insulin resistance plus low or high β-cell function

Insulin resistance plus low β-cell function was only observed in individuals with undiagnosed diabetes, and the prevalence was stable over time. However, insulin resistance plus high β-cell function was most frequently observed in individuals with prediabetes. There were increasing trends in both sexes (Supplemental Table 4).

Discussion

In this nationally representative study of US adults from 2001 to 2016, not only did the prevalence and absolute numbers of people with prediabetes grow substantially but the current analysis also showed that
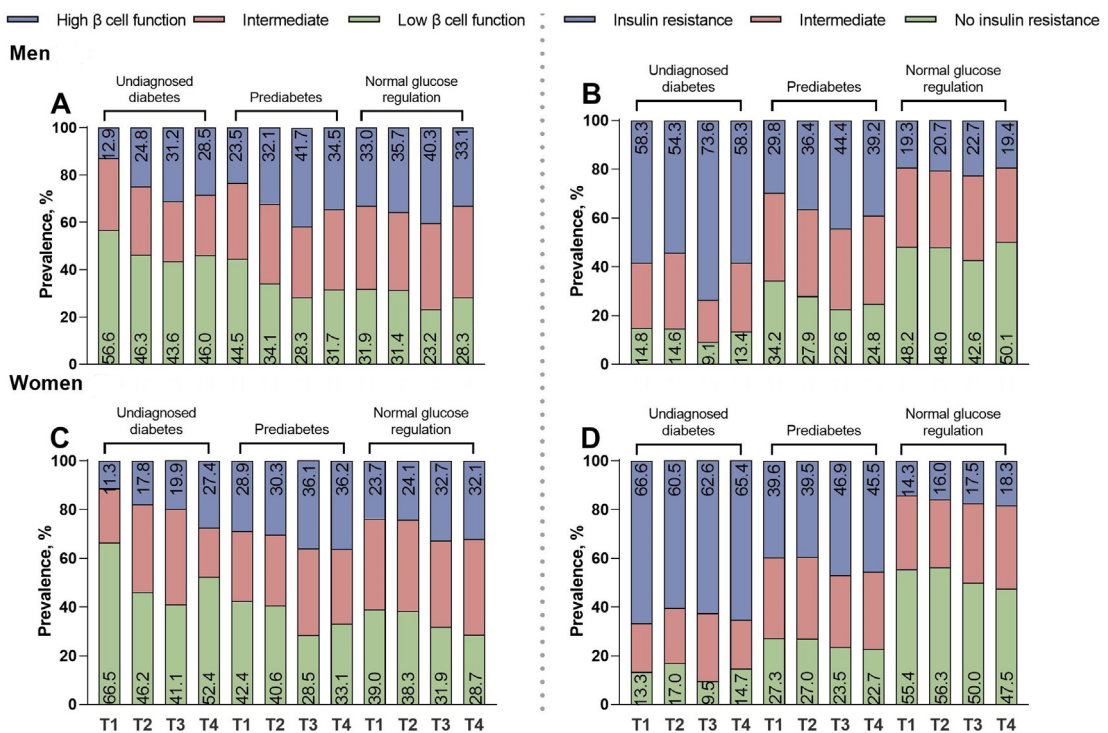

Fig. 1. Prevalence of low β cell function and insulin resistance by sex and glycemic status, 2001−2016 for men (A and B) and women (C and D). HOMA2%B and HOMA2IR were divided into sex-specific quartiles in participants without undiagnosed diabetes. We defined the upper tertile of HOMA2IR as indicative of insulin resistance, the mid tertile as indicative of intermediate condition, and the lower tertile as indicative of no insulin resistance. For β-cell function, the lower tertile was defined as low β-cell function, the mid tertile as intermediate β-cell function, and the upper tertile as high β-cell function. The cutoff values were also applied in undiagnosed diabetes. HOMA2%B: homoeostasis model assessment 2 for β-cell function; HOMA2IR: homoeostasis model assessment 2 for insulin resistance; T1−T4: Time cycle of study period 2001−2004, 2005−2008, 2009−2012, and 2013−2016.

Table 3
Association of insulin resistance and beta cell dysfunction with per 2 survey cycle increment by glycemic status.

Per 2 survey cycle increment	Model 1	Model 2	Model 3
Insulin resistance			
Men			
Undiagnosed diabetes	1.09 (0.85, 1.40)	1.12 (0.86, 1.46)	1.11 (0.79, 1.55)
Prediabetes	**1.15 (1.06, 1.25)**	**1.15 (1.05, 1.26)**	1.11 (0.99, 1.23)
NGR	1.01 (0.92, 1.10)	1.02 (0.93, 1.12)	1.02 (0.92, 1.14)
Women			
Undiagnosed diabetes	1.04 (0.83, 1.31)	0.99 (0.77, 1.28)	1.05 (0.78, 1.40)
Prediabetes	**1.11 (1.01, 1.22)**	**1.14 (1.04, 1.25)**	1.10 (0.98, 1.23)
NGR	1.10 (1.00, 1.22)	1.11 (0.98, 1.23)	1.04 (0.93, 1.16)
Low β cell function			
Men			
Undiagnosed diabetes	0.90 (0.73, 1.10)	0.88 (0.71,1.10)	0.92 (0.73, 1.17)
Prediabetes	**0.84 (0.77, 0.92)**	**0.84 (0.76, 0.92)**	**0.85 (0.77, 0.95)**
NGR	0.92 (0.83, 1.01)	0.91 (0.82, 1.01)	**0.87 (0.78, 0.97)**
Women			
Undiagnosed diabetes	0.95 (0.73, 1.24)	0.96 (0.74, 1.24)	0.90 (0.70, 1.16)
Prediabetes	**0.85 (0.77, 0.93)**	**0.83 (0.75, 0.91)**	**0.82 (0.73, 0.92)**
NGR	**0.85 (0.78, 0.91)**	**0.84 (0.78, 0.91)**	**0.87 (0.79, 0.95)**

Data are presented as odds ratios (95% confidence interval). The bold number indicated $P < 0.05$. Model 1 was unadjusted. Model 2 was adjusted for age, race, current smoking, education, at or below poverty line. Model 3 was adjusted for age, race, current smoking, education, at or below poverty line, and waist circumference. Logistic regression was used by including the midpoint of each survey period as a continuous variable. NGR: normal glucose regulation.

insulin resistance presented an increasing trend in both sexes individuals with prediabetes, while β-cell function was compensatorily elevated. Furthermore, adjusting for WC, but not BMI, could completely attenuate the significant trends in HOMA2IR in women and curb the trend in men with prediabetes to some extent. These findings highlights that there are quantitative (larger prediabetic population) and qualitative (deteriorating insulin resistance) changing trends in the context of prediabetes and reducing central obesity would probably curb the worsening condition.

The cardinal manifestations of insulin resistance are euglycemia or hyperglycemia with hyperinsulinemia. Insulin resistance is not just one major pathologic feature of type 2 diabetes. A very recent review proposed a novel cardiometabolic-based chronic disease model focusing on primary drivers (gene, environment and behavior), metabolic drivers, and subsequent cardiovascular endpoints, with insulin resistance as the central abnormality and the mechanism driving the progression.[7] Regarding its early role in the development of cardiovascular endpoints, in a meta-analysis including 516,325 adults without diabetes, the relative risk of coronary heart disease per standard deviation increase was 1.46 (95% CI 1.26, 1.69) for HOMAIR, which was much higher than that for glucose and fasting insulin.[18] The reason may be due to unfavorable effects of insulin resistance on endothelial dysfunction and inflammation. Insulin resistance could

inhibit phosphoinositide 3-kinase/Akt, which regulates endothelial nitric oxide synthase activity; activate mitogen-activated protein kinase signaling, which increases vasoconstrictor endothelin-1 expression,[19] and increase renin-angiotensin-aldosterone system activity.[20] Insulin resistance could also induce the release of proinflammatory cytokines from fat tissue, which promotes the formation of M1 macrophages, an essential process in atherosclerotic lesion progression.[21]

There was heterogeneity in sex-specific trends in insulin resistance and β-cell function. Women had higher HOMA2IR and lower HOMA2%B than men. Women are intrinsically more insulin resistant than men, possibly because of specific sex-linked gene expression and the resulting differences in metabolic control elements.[22] In the NGR group, women, but not men, also showed an increasing trend in HOMA2IR. However, in men with prediabetes, the degree of increases in HOMA2IR and insulin resistance was larger than that in women.

Finally, earlier intervention to stop or even reverse the current trends in insulin resistance is beneficial, but how may this be accomplished? It is well acknowledged that the high incidence and degree of insulin resistance is in great part due to the global epidemic of obesity.[23,24] Since 1999, the prevalence of central obesity has increased steadily, and by 2030, it is projected to reach 55.6% in men and 80.0% in women.[25]

Our results indicate that a reduction in WC could stop the significant increasing trends in insulin resistance in women and curb the trend in men to some extent. Based on previous evidence,[26,27] primordial prevention, especially control of central obesity, could attenuate abnormal adiposity, insulin resistance, subsequent compensatory insulin secretion, and adverse effects of hyperglycemia.[28] Furthermore, pharmacological interventions targeting insulin resistance, such as metformin and GLP-1 agonists, could also be considered. During a mean follow-up of 15 years, metformin was shown to reduce diabetes incidence by 18% in individuals with prediabetes compared with the placebo group,[26] metformin could also reduce coronary artery calcium incidence and severity in individuals with prediabetes.[29] Although those who have both insulin resistance and the poorest β-cell function are at highest risk for diabetes,[30] in our results, insulin resistance with compensatory insulin secretion was far more common in individuals with prediabetes. Therefore, we may consider that insulin resistance plays a central integrating pathophysiological role in cardiometabolic prevention,[28] early intervention would result in a great benefit.

This study has some limitations. First, the design of this study was cross-sectional; thus, the data could only explore secular trends but failed to provide longitudinal follow-up data. However, NHANES is a collection of continuous surveys offering important snapshots, and valuable information about two major pathological features of metabolic diseases in individuals with different glycemic statuses was provided over time. Second, HOMA indices were used as surrogate measures for insulin resistance and β-cell function instead of the sophisticated gold standard method of dynamic clamp testing. However, the clamp is not feasible in large epidemiological studies. We also used the updated HOMA2 nonlinear (computer) model that has been recalibrated in line with current insulin assays. There is good correlation between estimates from HOMA2 and the clamp/minimal model, and the coefficient could be 0.78–0.88 for HOMA2IR and 0.87–0.90 in HOMA2%B.[16,31,32] Third, the categorization of undiagnosed diabetes, prediabetes and NGR was based on a one-time measurement. This method might not be consistent with the relatively strict clinical diagnostic criteria and could result in a higher estimation of undiagnosed diabetes and prediabetes prevalence. However, in large epidemiological studies, definitions based on one-time measurements are commonly used. In NHANES, they were consistently used and calibrated in line through surveys, making our analyses internally

valid.[6] Also, we could not distinguish type 1 or type 2 diabetes based on available information.

Regarding strengths, our study used nationally representative data and sex-specific analyses. The NHANES is a series of meticulously conducted surveys with consistently high-quality control, ensuring that the data are obtained in a timely manner and are of high quality. When assessing trend significance, we adjusted the models to remove the effect of age, smoking, education, economic status, and weight indices across different glycemic groups. Additionally, we used continuous (HOMA2%B and HOMA2IR) and categorical (β-cell function and insulin resistance) variables to obtain a comprehensive figure of national trends over time.

In conclusion, this nationally representative study showed that from 2001 to 2016, insulin resistance demonstrated an increasing trend in both sexes with prediabetes, while β-cell function showed a compensatory increasing trend. WC could completely attenuate the significant trends in insulin resistance in women and partly in men. These data call for conceptualizing the prediabetes stage as a time for early intervention, and reducing insulin resistance via extensive lifestyle modification, especially by controlling central obesity and/or by implementing necessary pharmacologic measures.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cdtm.2020.11.003.

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