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Trends in the Burden of Non-alcoholic Fatty Liver Disease in a US Cohort of Veterans

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Abstract

Background & Aims—Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease in the United States (US). However, few data are available on recent trends in the incidence and prevalence of NAFLD in the US.

Methods—We analyzed the national Veterans Administration (VA) databases from 2003 to 2011 and calculated the age-adjusted prevalence and incidence of NAFLD for the overall sample of patients and by demographic subgroups. We used a previously validated algorithm to define

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NAFLD, based on persistent increases in levels of liver enzymes in the absence of positive results from tests for hepatitis C or hepatitis B, or evidence of excessive alcohol use.

Results—Of the 9,784,541 patients with at least 1 visit to the VA between 2003 and 2011, 1,330,600 patients (13.6%) had NAFLD. The annual incidence rates of NAFLD remained stable (from 2.2% to 3.2%) over the study duration. The prevalence of NAFLD increased from 6.3% in 2003 (95% confidence interval, 6.26%–6.3%) to 17.6% in 2011 (95% confidence interval, 17.58%–17.65%)—a 2.8-fold increase. The incidence and prevalence increased at significantly greater rates in patients younger than 45 years old vs older patients.

Conclusions—In a US population, the annual incidence of NAFLD ranges from 2% to 3%. The prevalence of NAFLD more than doubled from 2003 through 2011; it is likely to continue to increase, due to a steady overall incidence coupled with a rising incidence in younger individuals.

Keywords

Prevalence; incidence; epidemiology; metabolic syndrome; nonalcoholic fatty liver disease

BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) has become the leading cause of chronic liver disease in the U.S.¹ At least 20-30% of patients with NAFLD may develop progressive liver disease called nonalcoholic steatohepatitis (NASH) that can result in cirrhosis and related complications in 10-20% of cases.²⁻⁴ Despite an increasing recognition of NAFLD as the major cause of liver injury, few studies have systematically examined the temporal trends in its disease burden in the U.S.

Disease burden in chronic conditions like NAFLD is mostly reflected by its prevalence; however the prevalence itself is driven by the incidence as well as chronicity of the condition. Most available studies have examined prevalence of NAFLD at a single timepoint;⁴⁻⁶ only one study examined temporal trends in the prevalence,⁷ and none examined the incidence of NAFLD in a large U.S. cohort. Measuring the incidence rates and their recent temporal trends is important as these data can provide an insight into the future burden of NAFLD and help guide both clinicians and the health care system to develop strategies and capacity targeted towards providing timely and effective care.

The Veterans Administration (VA) is the largest integrated healthcare system in the U.S. It is a semi-closed system with a relatively stable patient population, making long-term studies possible. Using a national sample of VA users, we report changes in the annual incidence and prevalence of NAFLD between 2003 and 2011, both in the overall population of VA users as well as in different subgroups of interest.

METHODS

Data Source

We used VA national Corporate Data Warehouse (CDW) for this study. CDW data exist on the VA Informatics and Computing Infrastructure (VINCI) platform in a relational database.⁸ It includes all laboratory test results as well as inpatient and outpatient utilization

as indicated by procedure (CPT codes) and diagnosis (ICD-9 codes) codes. CDW also contains information from annual AUDIT-C screen for alcohol use disorders which has been used to screen over 90% of VA outpatients nationwide.⁹ A score of 4 is used to identify active alcohol use in men and 3 is used in women.¹⁰

Study Cohort and NAFLD Patient Identification

We evaluated all patients who had at least one visit to the VA between January 1, 2003 and December 31, 2011 for the presence of NAFLD. We defined NAFLD based on our previously validated algorithm.¹¹ Specifically, patients were classified as having NAFLD if they had at had two or more elevated ALT values (≥ 40 IU/ml) more than 6 months apart, with no evidence of positive serologic testing for HBV (HBV surface antigen) or HCV (HCV RNA), and no alcohol related ICD-9 codes or positive AUDIT-C scores within one year of the elevated ALT. This definition had good sensitivity and specificity for identifying NAFLD compared to clinical, biochemical and radiological data abstracted from the electronic medical record review of 600 VA patients (sensitivity=78.4%, negative predictive value= 85.6%).¹¹ We used the date of first elevated ALT as the index date for NAFLD diagnosis. For all patients in this cohort, we extended follow-up through December 31, 2013 to allow sufficient time for ascertainment of persistence in ALT elevation (see below), and we examined data from January 1, 2001 to December 31, 2002 to exclude patients with prevalent or pre-existing ALT elevations from incidence calculations.

To examine the robustness of the findings in a sensitivity analysis, we used a more *restrictive* NAFLD definition that classified patients as NAFLD if the elevated ALT test was performed in ambulatory settings with evidence of persistence elevation for at-least 2 years; this definition had specificity of 92.4%, a positive predictive value of 80.8% but a sensitivity of 55.0% in our validation study.¹¹

Demographic variables—These variables included age at each calendar year (20-44, 45-64, and ≥ 65 years),¹² race/ethnicity (non-Hispanic white, non-Hispanic black and Hispanic), and gender. We included other racial/ethnic groups in the total counts but did not analyze them separately because of small sample sizes.

Statistical Analyses

We calculated the incidence and prevalence of NAFLD in successive cross-sectional cohorts for each calendar year from 2003 to 2011.

We considered NAFLD patients with the first evidence of elevated ALT in a given year as incident cases for that year. We calculated the calendar-year specific incidence rates of NAFLD by dividing the number of patients with new NAFLD in a calendar year by the total number of patients with at least one inpatient or outpatient visit to the VA in the same year excluding those who met the criteria for NAFLD in the previous years as far back as 2001. We calculated calendar-year specific prevalence as the number of patients meeting the NAFLD definition either *before* (starting with 2001) or *during* a calendar year divided by the total number of patients with at least one visit to the VA during that year. We also calculated 95% confidence intervals (CI) for the incidence and prevalence estimates.

We examined temporal trends in NAFLD incidence and prevalence in the overall population and in the demographic subgroups (age, race/ethnicity, gender). We adjusted for possible variations over time in the age distribution of the eligible underlying population by calculating age-standardized rates for the overall population as well as race/ethnicity and gender subgroups using the direct standardization method with 10 year age strata. We used the age distribution of the 2003 VA population as the standard population. Because analysis of time trends depends on the initial time point of examination, we used a latter year (2004) as the starting point in a sensitivity analysis and examined the estimates of time trends.

To analyze temporal trends in incidence and prevalence, we used freely available Joinpoint Regression software, version 4.1.1 (National Cancer Institute: <http://surveillance.cancer.gov/joinpoint/>). Briefly, Joinpoint is a piecewise linear regression analysis that uses statistical criteria that determines the minimum number of linear segments needed to describe a trend; the points at which a segment begins and ends; the annual percentage change (APC) along with 95% confidence interval (CI) for each segment; and whether the APC is significantly different from 0.¹³ We also computed the average APC (AAPC) as a weighted average of the APC's from the Joinpoint model, with the weights equal to the length of the APC intervals.¹⁴ We compared the trends between two subgroups by employing a test of parallelism using the permutation test. In instances where the trends were significantly different (using an *a-priori* cut off <0.05), we used a z test to compare the AAPC between the subgroups.¹⁵

Last, we examined the prevalence of advanced fibrosis in patients with NAFLD by calculating NAFLD fibrosis score (FS) for all NAFLD patients who visited the VA in 2011. We calculated the prevalence of advanced fibrosis as the number of NAFLD patients with NAFLD-FS ≥ 0.676 divided by the total number of NAFLD patients with at least one visit to the VA during 2011. NAFLD-FS accurately separates between NAFLD patients with and without advanced fibrosis/cirrhosis.¹⁶ It is calculated based on age, BMI, diabetes, AST/ALT, platelets, and albumin. We defined diabetes based on ≥ 1 ICD-9 codes for diabetes and used the latest value available between 1/1/2010 and 12/31/2011 to derive patients' age, BMI, AST, ALT, platelets and albumin data.

RESULTS

Study Cohort

We identified 9,784,541 patients who were seen either in outpatient or inpatient clinics at the VA between 1/1/2003 and 12/31/2011. Of these, 1,330,600 patients had NAFLD based on our primary definition (at-least two ALT values that were ≥ 40 IU/ml at least 6 months apart, no positive tests for HBV or HCV, and no heavy alcohol use within one year of first elevated ALT). Using our more restrictive NAFLD definition (elevated ALT values in an ambulatory setting, at least 6 months apart *but* within 2 years of each other) resulted in 825,722 patients with NAFLD.

Demographic Characteristics of Underlying Eligible Population

The number of patients who visited the VA in each of the study calendar years increased from 4,694,585 in 2003 to 5,675,844 in 2011. The VA patient population became younger

between 2003 and 2011. Specifically, the annual proportion of patients 45 years or younger increased from 7.6% in 2003 to 18.2% in 2011 (**Table 1**). The racial distribution of patients with known race remained fairly stable over time, with the annual proportion of patients with missing race data decreasing over time. Similarly, the gender distribution remained stable over time.

NAFLD Trends for Total Population

Figure 1 shows the temporal trends of age-adjusted incidence and prevalence rates of NAFLD in the overall population. The number of incident cases of NAFLD ranged from 116,000 to 145,000 per year. The incidence rate per 100 persons was 3.16 (95% CI: 3.14 to 3.17) in 2003, remained between 2.3 to 2.7 for most of the study years, and declined slightly to 2.5 (95% CI: 2.49 to 2.52) in 2011 (APC -3.2, 95% CI: -5.0 to -1.4, $p=0.004$) (**Table 2**). Using 2004 as the initial point of the study attenuated but did not eliminate the downward trend in NAFLD incidence seen in the primary analysis that used 2003 as the starting point (APC -2.6%, 95% CI: -4.8 to -0.4%, $p=0.03$) (**Appendix Figure 1**).

The number of prevalent cases of NAFLD increased from 294,895 in 2003 to 1,079,531 in 2011. The age-adjusted prevalence per 100 persons increased by 2.8-fold from 6.28 (95% CI: 6.26 to 6.30) in 2003 to 17.61 (95% CI: 17.58 to 17.65) in 2011. (**Figure 1**). The prevalence increased sharply during 2003-2005 (APC 28.3%, 95% CI: 16.0 to 42.0%, $p=0.02$), rose more slowly during 2005-2008 (APC 12.9%, 95% CI: 4.9 to 21.5%, $p=0.03$) and during 2008-2011 (APC 5.4%, 95% CI: 2.2 to 8.6%, $p=0.03$). The AAPC for overall prevalence was 13.6% (95% CI: 12.9 to 14.3%) for the entire study duration (**Table 3**).

Using the more restrictive and specific definition of NAFLD resulted in lower estimates for incidence and prevalence, although the temporal trends remained similar to those described above. Specifically, the incidence rates of NAFLD ranged from 2.52 per 100 persons (95% CI: 2.51 to 2.54) in 2003 to 1.30 (95% CI: 1.29 to 1.31) in 2011. The prevalence per 100 persons increased from 5.31 (95% CI: 5.29 to 5.33) in 2003 to 10.93 (95% CI: 10.90 to 10.96) in 2011. The AAPC for both incidence (-7.5%, 95% CI: -13.9, -0.5%) and prevalence (9.1%, 95% CI: 8.1 - 10.1%) trends were similar to that of the primary NAFLD definition (**Appendix Figure 2**).

Temporal Trends for NAFLD According to Demographic Subpopulations

The incidence rate of NAFLD was the highest in the 45-64 year group for most years, ranging from 3.3 to 4.2 per 100 persons (**Figure 2** and **Table 2**). However, the greatest increase in incidence was observed in persons younger than 45 years old. Specifically, the annual incidence in younger patients increased from 2.3 in 2003 to 4.3 per 100 persons in 2011 (APC 7.4%, 95% CI: 5.7 to 9.2%) – a trend that was significantly different than the trends in 45 to 64 year olds (difference in AAPC 9.1%, 95% CI: 6.8 to 10.9%) and 65 year and older patients (difference in AAPC 14.2%, 95% CI: 12.0 to 16.2%), respectively (**Appendix Table 1**).

Hispanics had the highest and African Americans had the lowest incidence rates for NAFLD across all study years whereas the rates among non-Hispanic whites fell in between. For

example, in 2011, NAFLD incidence was 3.41 per 100 persons (95% CI: 3.33 to 3.49) in Hispanics, 2.99 per 100 persons (95% CI: 2.97 to 3.01) in non-Hispanic whites, and 2.44 (95% CI: 2.40 to 2.48) per 100 persons in African Americans. NAFLD incidence was lower in women than in men across all years. Despite these differences in the incidence rates at any given time point, the temporal trends in the incidence of NAFLD were similar across racial subgroups and in both genders (p-value for test for parallelism >0.05) (**Appendix Table 1**).

There were also differences in the NAFLD prevalence by age, race, and gender; with rates being higher in older patients, Hispanics, and in men (**Figure 2** and **Table 3**). However, the trends for prevalence in many subgroups were similar to the overall trend, with prevalence increasing at a similar rate in all racial/ethnic groups during the study period. In contrast, prevalence increased disproportionately in patients younger than 45 year (differences in AAPC, 4.4%; 95% CI: 2.4 to 5.3% when compared to 45 to 64 year olds; and 2.7%, 95% CI: 1.2 to 3.5% compared to 65 years and older) and among women (difference in AAPC between women and men=6.6%, 95% CI: 3.3 to 8.0) (**Appendix Table 2**).

A total of 76.5% of NAFLD patients who sought care in the national VA in 2011 had sufficient data to allow the calculation of NAFLD-FS. Of these, 174495 (21.3%) patients had NAFLD-FS 0.676 and thus were at high risk for advanced fibrosis. NAFLD-FS was in the indeterminate range for 49.6% and <-1.455 in 29.1% of NAFLD patients seen in 2011.

DISCUSSION

In this analysis of a large, demographically and geographically diverse group of patients seen in the national VA system, we found that the prevalence of NAFLD increased by a factor of 2.8 in just 9 years between 2003 and 2011. This increase was evident in all racial groups, across all age groups, and in both genders. Furthermore, approximately one in five patients with NAFLD who visited the VA in 2011 was at risk for advanced fibrosis. The annual incidence of NAFLD ranged between 2 to 3%, translating into 116,000 to 145,000 new cases who met the study criteria for NAFLD each year. Collectively, the increase in NAFLD prevalence combined with a steady total number of incident or new cases annually suggests that NAFLD will continue to remain a major public health problem in the U.S. at least in the near and intermediate future.

Our analysis also identified emergent subgroups at particular risk for NAFLD. For example, despite the generally stable incidence of NAFLD in many subgroups, we found a strong and upward trend in NAFLD incidence and prevalence among individuals younger than 45 years, a finding consistent with previous reports.¹² Similarly, the rate of increase in the prevalence of NAFLD was greater in women than in men. We also found substantial differences in the prevalence of NAFLD among various racial/ethnic groups, and these results extend the findings of recent studies.^{6,7} For example, by 2011, more than 21% of Hispanic patients seen in the national VA met the criteria for NAFLD compared to 19.8% of whites and 16.9% of African Americans. These data underscore the importance of effective prevention and management programs targeting these high risk individuals.

Our results also shed some light on the potential long term burden of NAFLD. Despite the rise that we observed overall, our analysis suggests that the rate of increase in NAFLD prevalence may be slowing down in the more recent years. This trend can be attributed to a potential decline in the incidence rate of NAFLD. Specifically, we found that the annual incidence of NAFLD fell from 3.2 in 2003 to 2.5 per 100 persons in 2011. It is difficult for us to discern the reasons for this deceleration. Although recent studies show that the rate of increase in both obesity and diabetes – both major risk factors for NAFLD – may be slowing down in the U.S.^{12,17} this may not be the case in the VA where the prevalence of obesity and diabetes is in fact higher than in the U.S. population. Although interesting and potentially important, monitoring of these trends with longer period of follow up is required to confirm these early findings.

The prevalence of NAFLD was somewhat lower in our analysis compared to the previously reported estimates and this is likely related to our case definition. Previous studies relying on liver biopsy, abdominal ultrasound, and magnetic resonance imaging estimated the general population prevalence of NAFLD at ~30%.⁴⁻⁶ None of these methods are feasible in determining incidence of NAFLD because they need to be applied to several million individuals repeatedly over time. We used clinical and lab criteria to define NAFLD. Most clinicians rely on these readily available noninvasive test criteria—such as elevated blood levels of ALT in the absence of other liver diseases to detect NAFLD and our previous work provided support for the validity of our algorithm.¹¹ We recognize that NAFLD can exist in the absence of elevated ALT⁶ and that we may have missed individuals who have some evidence of hepatic steatosis yet have never developed abnormal liver biochemistries. Of note, most of the available literature on the prevalence of elevated ALT in NAFLD stems from cross-sectional studies (where ALT tests were performed at one point in time) in which it was unknown if patients classified as having normal ALT based on these single assessments maintain normal biochemistries throughout their clinical course. Indeed, the American Association for the Study of Liver Disease recommends against routine evaluation of individuals (even those with incidental findings of hepatic steatosis) unless they have abnormal liver biochemistries or evidence of progressive disease. We believe that our case definition for NAFLD captures those with clinically apparent and relevant NAFLD; the majority of whom remain unrecognized and undiagnosed in routine practice.¹⁸ It is possible that some patients with clinically significant NAFLD may have persistently normal biochemistries during their entire clinical course at the VA, particularly if early in the disease process or if they were first seen at the VA towards the end of our study period, and we missed these patients. We also excluded HCV and HBV cases with coexistent NAFLD, thus likely underestimating the true burden of NAFLD.

Our study has several limitations. We did not analyze care that occurred before January 1, 2001, and some patients, particularly those included in the database during the earlier years, might have had ALT elevations before 2001. However, we accounted for this possibility in our analysis plan and examined it further in a sensitivity analysis (changing the starting point from 2003 to 2004) and believe that this effect is likely small. We are also limited by the sensitivity and specificity of the NAFLD algorithm that we used in this study. Because our goal was to understand the burden of disease as well as identify subgroups at risk for NAFLD, we purposely used a less restrictive definition (with higher sensitivity and negative

predictive value) for the primary analysis but used a more specific definition to provide the full range of the incidence and prevalence estimates. We used a relatively high cut-off value for ALT to define NAFLD. However, our cut-off criteria is consistent with recommendations from previous population based analyses suggesting use of a higher cut-off (~44 IU/ml) in low risk (non-HCV) populations.¹⁹ Similarly, although gender specific cut-offs are not absolutely necessary for large screening studies, we likely underestimated the incidence and prevalence of NAFLD in women because women tend have lower ALT values than men.¹⁹ Last, our findings may have limited generalizability as they are derived from the VA population. The prevalence of obesity and diabetes among Veterans using the VA for their healthcare is likely higher than in the general population.^{20,21} Nonetheless, the temporal trends that we observed are likely generalizable to non-Veterans. Indeed, Ruhl *et al.* found very similar trend in the prevalence of NAFLD using data from the National Health and Nutrition Examination Survey.⁷ Furthermore, our study is important in and of itself because it provides the first data on the incidence and prevalence of NAFLD in the VA. The VA is the largest integrated healthcare system in the U.S. We believe that the sheer size of the Veteran cohort combined with a complete dearth of information regarding the burden of NAFLD in the VA renders our findings highly significant. Furthermore, VA is in a unique position to test and implement systemic changes in medical care delivery to improve the health care of NAFLD patients.

In conclusion, we found that the annual incidence of NAFLD ranged between 2 to 3%, slightly decreased from 2003 to 2011 in the overall cohort, but was increasing in individuals younger than 45 years old. The prevalence more than doubled from 2003 to 2011, albeit at a lower rate during the more recent years, and with increased prevalence found in all racial groups as well as in both genders. The prevalence of NAFLD is likely to continue to rise in the near term due to a fairly steady incidence overall combined with a rising incidence in younger individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Temporal trends in the age adjusted incidence (1A) and prevalence (1B) of non-alcoholic fatty liver disease - 2003 and 2011.

Figure 2. Trends in the age adjusted (for race and sex) incidence and prevalence of non-alcoholic fatty liver disease among various subgroups of individuals - 2003 and 2011

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Table 1

Demographic characteristics of annual cohorts from 2003 to 2011

	2003		2004		2005		2006		2007		2008		2009		2010		2011	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age group, years																		
<45	355637	7.6	413754	8.5	471068	9.4	532138	10.5	607164	11.9	702619	13.6	815444	15.3	926517	16.8	1035740	18.2
45-65	1614051	34.4	1735546	35.6	1828034	36.6	1913299	37.7	2006041	39.2	2117502	40.8	2275285	42.6	2432672	44.0	2569528	45.3
>=65	2724897	58.0	2723544	55.9	2701189	54.0	2632995	51.8	2501177	48.9	2366184	45.6	2250025	42.1	2168925	39.2	2070576	36.5
Gender																		
Female	380011	8.2	394872	8.2	403830	8.2	417785	8.3	428841	8.5	453943	8.9	469615	9.1	480248	8.9	502177	9.1
Male	4251208	91.8	4415860	91.8	4535130	91.8	4599132	91.7	4620151	91.5	4648932	91.1	4695465	90.9	4897221	91.1	5031945	90.9
Race/Ethnicity*																		
White	2435440	51.9	2662166	54.6	2828201	56.6	2955685	58.2	3023188	59.1	3083693	59.5	3196404	59.8	3341188	60.4	3442444	60.6
Black	503040	10.7	544918	11.2	574233	11.5	592807	11.7	614283	12.0	640066	12.3	676766	12.7	715852	13.0	748865	13.2
Hispanic	158612	3.4	177254	3.6	190024	3.8	201301	4.0	210333	4.1	220875	4.3	233792	4.4	246956	4.5	260278	4.6
Other	68184	1.4	76342	1.6	81530	1.6	85146	1.7	89747	1.8	94242	1.8	99507	1.9	105893	1.9	111893	2.0
Unknown	1529309	32.6	1412164	29.0	1326303	26.5	1243493	24.5	1176831	23.0	1147429	22.1	1134285	21.2	1118225	20.2	1112364	19.6

Temporal trends in the age adjusted incidence of non-alcoholic fatty liver disease in total population and in demographic subpopulations - 2003 and 2011

Table 2

	2003		2011		APC (95% CI)	APC p-value
	Case N	% (95% CI)	Case N	% (95% CI)		
Total	142665	3.16 (3.14, 3.17)	145147	2.51 (2.49, 2.52)	-3.2 (-5.0, -1.4)	0.004
Age group[*], years						
<45	8085	2.32 (2.27, 2.37)	38957	4.26 (4.22, 4.30)	7.4 (5.7, 9.2)	<0.001
45-64	65011	4.21 (4.18, 4.24)	78958	3.83 (3.80, 3.85)	-1.7 (-3.6, 0.2)	0.08
≥65	69569	2.63 (2.61, 2.65)	27232	1.54 (1.53, 1.56)	-6.7 (-8.5, -4.9)	<0.001
Gender						
Female	4366	1.27 (1.23, 1.30)	7613	1.41 (1.38, 1.45)	1.0 (-0.8, 2.9)	0.23
Male	135744	3.35 (3.33, 3.37)	132340	2.65 (2.63, 2.66)	-3.4 (-5.1, -1.6)	0.003
Race/ethnicity						
White	91649	3.88 (3.86, 3.91)	98964	2.99 (2.97, 3.01)	-3.5 (-5.4, -1.6)	0.003
Black	16573	3.33 (3.28, 3.38)	19246	2.44 (2.40, 2.48)	-3.4 (-6.2, -0.4)	0.03
Hispanic	6279	3.88 (3.78, 3.98)	9256	3.41 (3.33, 3.49)	-1.6 (-2.7, -0.4)	0.02

* Not age-adjusted since they are stratified by age groups

Table 3

Temporal trends in the age adjusted prevalence of non-alcoholic fatty liver disease in total population and in demographic subpopulations - 2003 and 2011

	2003			2011			p-value	Period1	APC1 (95% CI)	p-value	Period2	APC2 (95% CI)	p-value	Period3	APC3 (95% CI)	p-value	AAPC [‡] (95% CI)
	N	% (95% CI)	N	% (95% CI)													
Total	294895	6.28 (6.26, 6.30)	1079531	17.61 (17.58, 17.65)	2003-2005	2003-2006	2003-2005	28.3 (16.0, 42.0)	0.02	2005-2008	12.9 (4.9, 21.5)	0.03	2008-2011	5.4 (2.2, 8.6)	0.03	13.6 (12.9,14.3)	
Age group*, year																	
< 45	147302	4.14 (4.08, 4.21)	159959	15.44 (15.37, 15.52)	2003-2006	2003-2006	2003-2006	27.7 (22.6, 33.0)	<0.001	2006-2011	11.8 (10.8, 12.7)	<0.001	---	---	---	17.5 (16.1, 18.8)	
45 to 64	135308	8.38 (8.34, 8.43)	585432	22.78 (22.73, 22.84)	2003-2006	2003-2006	2003-2006	24.5 (20.5, 28.5)	<0.001	2006-2011	6.7 (5.7, 7.7)	<0.001	---	---	---	13.0 (12.0, 14.1)	
65	144854	5.32 (5.29, 5.34)	334140	16.14 (16.08, 16.19)	2003-2005	2003-2005	2003-2005	29.1 (28.5, 29.7)	<0.001	2005-2008	14.6 (14.2, 15.0)	<0.001	2008-2011	6.2 (6.1, 6.4)	<0.001	14.75 (14.72, 14.78)	
Gender																	
Female	84007	2.45 (2.40, 2.50)	44430	10.66 (10.57, 10.75)	2003-2005	2003-2005	2003-2005	38.6 (−1.2, 94.4)	0.05	2005-2008	18.2 (−5.2, 47.4)	0.07	2008-2011	10.8 (2.0, 20.3)	0.04	20.0 (17.8, 22.3)	
Male	279841	6.62 (6.60, 6.64)	1009221	18.33 (18.29, 18.37)	2003-2005	2003-2005	2003-2005	28.0 (1.9, 60.7)	0.05	2005-2008	13.2 (−4.0, 33.6)	0.07	2008-2011	4.9 (−2.2, 12.5)	0.07	13.4 (11.9, 15.0)	
Race/ethnicity																	
White	189025	7.64 (7.60, 7.67)	740949	19.83 (19.78, 19.87)	2003-2005	2003-2005	2003-2005	25.8 (6.0, 49.4)	0.04	2005-2008	12.1 (−0.6, 26.5)	0.05	2008-2011	4.8 (−0.4, 10.2)	0.05	12.5 (11.4, 13.6)	
Black	34398	6.76 (6.69, 6.83)	131701	16.94 (16.85, 17.04)	2003-2006	2003-2006	2003-2006	20.1 (17.3, 23.0)	<0.001	2006-2011	7.4 (6.7, 8.2)	<0.001	---	---	---	12.0 (11.2, 12.8)	
Hispanic	13045	7.71 (7.58, 7.85)	61399	21.96 (21.78, 22.14)	2003-2005	2003-2005	2003-2005	26.6 (21.6, 31.8)	0.009	2005-2008	13.3 (10.2, 16.4)	0.01	2008-2011	6.4 (5.3, 7.6)	0.009	13.8 (13.5, 14.1)	

* Not age-adjusted since they are stratified by age groups

‡ All p-values for AAPC were <0.001