



## ORIGINAL ARTICLE

# Recent trends in the prevalence of type 2 diabetes and the association with abdominal obesity lead to growing health disparities in the USA: An analysis of the NHANES surveys from 1999 to 2014

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**Aim:** To assess whether the secular trends in type 2 diabetes prevalence differ between abdominally obese and non-obese individuals.

**Methods:** Data from the National Health and Nutrition Examination Surveys (NHANES) were used to estimate the prevalence of type 2 diabetes and abdominal obesity among individuals aged  $\geq 20$  years in the USA from 1999/2000 to 2013/2014, after standardization to the age, sex and ethnicity population distribution estimates on January 1, 2014, as published by the US Census Bureau.

**Results:** The prevalence of abdominal obesity in the US population increased from 47.4% (95% confidence interval [CI] 42.6–52.2) in 1999/2000 to 57.2% (95% CI 55.9–58.5) in 2013/2014. A significant increase was observed in all age groups: 20 to 44, 45 to 64, and  $\geq 65$  years. The prevalence of type 2 diabetes has also increased from 8.8% (95% CI 7.2–10.4) in 1999/2000 to 11.7% (95% CI 10.9–12.6) in 2013/2014, with no substantial change in trend over the recent years. However, the increase in the prevalence of type 2 diabetes was limited to individuals with abdominal obesity, and more specifically to individuals aged  $\geq 45$  years with abdominal obesity, with no significant change in prevalence in the non-obese group and in individuals aged  $< 45$  years.

**Conclusion:** These findings highlight the critical importance of abdominal obesity—both as a likely key contributor to the continuing epidemic of type 2 diabetes in the USA and as a priority target for public health interventions.

## KEYWORDS

database research, population study, type 2 diabetes

## 1 | INTRODUCTION

The prevalence rates of obesity and type 2 diabetes have increased concomitantly in the USA during the last 30 years.<sup>1–3</sup> Obesity, and in particular abdominal obesity, is also a major risk factor for type

2 diabetes,<sup>4,5</sup> suggesting that the increase in the prevalence of obesity has contributed, at least in part, to the increase in the prevalence of type 2 diabetes. The aims of the present study were to assess the trends in the prevalence of type 2 diabetes and abdominal obesity in the USA from 1999 to 2014, and to examine whether the trends in the prevalence of type 2 diabetes differ between abdominally obese and non-obese individuals. Our hypothesis was that the association between obesity and type 2 diabetes was contributing to growing health

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disparities and could justify more focused primary prevention programmes, for instance, targeting US residents presenting with obesity.

## 2 | METHODS

The National Health and Nutrition Examination Survey (NHANES) is a programme of studies designed to assess the health and nutritional status of adults and children in the USA. It has been conducted by the Centers for Disease Control and Prevention since the early 1960s. Beginning in 1999, every 2 years, NHANES examined a nationally representative sample of ~10 000 individuals from the resident, civilian, non-institutionalized US population. The survey consisted of an interview conducted in the home, followed the next day by a standardized health examination in specially equipped mobile examination centres that included a physical examination administered by trained medical personnel as well as laboratory tests.

Whole-blood specimens were drawn from all participants aged  $\geq 12$  years, then processed and stored under appropriate refrigerated ( $5^{\circ}\text{C}$ ) conditions. Specimens collected in 2013 to 2014 were shipped to the University of Missouri-Columbia for measurement of glycated haemoglobin (HbA1c) using the Tosoh G8 Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco, California). There have been changes in the equipment and location since 1999; however, NHANES recommends using the original data, without a cross-over study regression equation, for all analyses, including trend analyses. Abdominal circumference was measured with a tape drawn just above the uppermost lateral border of the right and left ilia. More information about data collection methods as well as the complex sampling design are available elsewhere (<http://www.cdc.gov/nchs/nhanes.htm>).

The population eligible for the present analysis consisted of individuals aged  $\geq 20$  years enrolled in any of the eight 2-year surveys conducted from 1999/2000 to 2013/2014. NHANES 2013/2014 was the latest survey with publicly available data at the date of download (February 27, 2017). Pregnant women were excluded.

Type 2 diabetes was identified when the NHANES participant answered yes to the question: "Other than during pregnancy, have you ever been told by a doctor or another health professional that you have diabetes or sugar diabetes?", or when HbA1c was  $\geq 6.5\%$ . Participants diagnosed with diabetes at age  $< 30$  years who required insulin therapy were assumed to have type 1 diabetes and were excluded from the type 2 diabetes population. Abdominal obesity was defined as waist circumference  $> 102$  cm for men and  $> 88$  cm for women.<sup>4</sup> For sensitivity analyses, overweight and obesity were also defined as body mass index (BMI)  $\geq 25$  and  $30$  kg/m<sup>2</sup>, respectively.

Other variables retained for analysis were sex, age in years, grouped as 20 to 44, 45 to 64, and  $\geq 65$  years, and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic and other).

Statistical procedures were conducted with SAS version 9.4 software (SAS Institute, Inc., Cary, North Carolina), with sampling weights provided by NHANES, accounting for the stratified, clustered sample design. Estimates were standardized according to the distributions of the non-institutionalized population of the USA by age group, sex and race/ethnicity on January 1, 2014, as per estimations from the US Census Bureau. Time trends for the prevalence of type 2 diabetes

and obesity were assessed using logistic regression models, and for the mean waist circumference using linear regression models, with the year of the survey entered as a continuous variable, from 0 for NHANES 1999/2000 to 14 for NHANES 2013/2014. Interactions with age were estimated in the full dataset, with age group considered as an ordinal variable. Sensitivity analyses were conducted to assess secular trends in the prevalence of abdominal obesity and type 2 diabetes by race/ethnicity.

NHANES was approved by the National Center for Health Statistics Research Ethics Review Board. All adult participants provided written informed consent.

## 3 | RESULTS

The size of the resident, non-institutionalized population of the USA (Table S1) increased from 272.2 to 311.2 million from January 1, 2000 to January 1, 2014, with a population that has become ethnically more diverse: of 230.6 million non-institutionalized US residents aged  $\geq 20$  years on January 1, 2014, 151.9 million (66%) were non-Hispanic white, 26.7 million (12%) were non-Hispanic black, 34.5 million (15%) were Hispanic, and 17.5 million (7%) were from another race or ethnicity. The size of the sample screened for NHANES increased from 12 160 in 1999/2000 to 14 332 in 2013/2014, with a response rate (NHANES participants over screened sample) that decreased from 82% in 1999/2000 to 71% in 2013/2014, but remained consistently higher than 70%. After exclusion of pregnant women and individuals aged  $\leq 20$  years, about one-half of the NHANES participants were eligible for analysis. More than 90% of the eligible participants (38 234/42 377) were retained for analysis. The most frequent reason for exclusion was missing HbA1c data. The frequency of missing data decreased continuously from 14% in 1999/2000 to 7% in 2013/2014, and the proportion of NHANES participants with missing HbA1c was not significantly associated with a prior diagnosis of diabetes (Table S2).

The prevalence of type 2 diabetes and abdominal obesity (Table 1) increased significantly between 1999/2000 and 2013/2014 from 8.8% (95% confidence interval [CI] 7.2-10.4) to 11.7% (95% CI 10.9-12.6) for type 2 diabetes, and from 47.4% (95% CI 42.6-52.2) to 57.2% (95% CI 55.9-58.5) for abdominal obesity ( $P < .001$  for both), after standardization to the age, sex, and race/ethnicity distributions in 2014. The prevalence of diabetes increased significantly among US residents aged  $\geq 45$  years, but no significant time trend was observed among individuals aged 20 to 44 years, while the prevalence of abdominal obesity increased in all age groups.

The prevalence of diabetes remained stable among non-obese individuals, with a mean annual change from 1999/2000 to 2013/2014 of 0.00% (95% CI -0.09 to 0.09;  $P = .80$  [Table 2]), whereas it increased significantly among abdominally obese individuals, with an annual percentage change of 0.22% (95% CI 0.08-0.36;  $P < .01$ ). This trend in abdominally obese individuals widened with age, as the annual percentage change increased from 0.05% (95% CI -0.09 to 0.20) in individuals aged 20 to 44 years to 0.31% (95% CI 0.09-0.54) in those aged 45 to 64 years and 0.48% (95% CI 0.18-0.78) in those aged  $\geq 65$  years ( $P$  value for the interaction term  $< .01$ ). These diverging trends resulted in larger

**TABLE 1** Prevalence of type 2 diabetes and abdominal obesity from 1999/2000 to 2013/2014, stratified by age group

	Prevalence of type 2 diabetes and abdominal obesity, % (95% CI)										Mean change per year
	1999/2000	2001/2002	2003/2004	2005/2006	2007/2008	2009/2010	2011/2012	2013/2014			
Type 2 diabetes	3959	4492	4316	4189	5300	5684	4966	5328			
20–44 years	2.3(1.4;3.1)n = 1614	3.4(2.0;4.8)n = 1892	2.8(1.8;3.8)n = 1746	3.2(2.1;4.4)n = 1794	2.6(1.8;3.4)n = 2080	2.5(1.7;3.3)n = 2381	3.5(2.5;4.5)n = 2141	3.3(2.6;4.0)n = 2265			0.04(–0.03;0.10)
45–64 years	11.8(9.5;14.2)n = 1224	11.8(9.0;14.7)n = 1417	13.2(11.0;15.3)n = 1262	13.0(10.7;15.2)n = 1329	14.3(11.7;16.9)n = 1845	13.3(11.4;15.2)n = 1925	14.3(11.8;16.8)n = 1733	15.5(13.1;17.8)n = 1846			0.24(0.06;0.41)
≥65 years	18.4(14.2;22.6)n = 1121	18.5(15.9;21.1)n = 1183	22.5(18.3;26.6)n = 1308	20.9(18.3;23.4)n = 1066	24.7(20.6;28.8)n = 1375	25.7(22.6;28.7)n = 1378	22.4(19.5;25.3)n = 1092	24.6(22.2;27.0)n = 1217			0.46(0.23;0.69)
<b>Total population</b>	<b>8.8(7.2–10.4)</b>	<b>9.3(7.8–10.8)</b>	<b>10.3(8.9–11.7)</b>	<b>10.1(8.8–11.4)</b>	<b>11.0(9.5–12.6)</b>	<b>10.8(9.8–11.8)</b>	<b>11.0(9.5–12.5)</b>	<b>11.7(10.9–12.6)</b>			<b>0.19(0.09–0.28)</b>
Abdominal obesity	3847	4296	4110	4014	5062	5421	4709	5059			
20–44 years	36.5(32.0;41.1)n = 1582	36.6(34.5;38.7)n = 1835	41.8(38.3;45.3)n = 1684	42.2(37.4;46.9)n = 1741	42.2(38.4;45.9)n = 2017	42.3(38.4;46.3)n = 2298	43.8(39.1;48.5)n = 2064	48.1(45.8;50.4)n = 2193			0.71(0.45;0.97)
45–64 years	54.5(48.3;60.7)n = 1200	56.6(53.1;60.1)n = 1378	61.0(57.6;64.4)n = 1225	58.9(54.5;63.4)n = 1294	60.5(56.6;64.4)n = 1778	61.5(57.7;65.2)n = 1856	63.4(58.8;68.0)n = 1661	62.3(59.7;64.9)n = 1768			0.55(0.23;0.86)
≥65 years	60.0(55.1;64.8)n = 1065	62.5(59.3;65.7)n = 1083	67.0(62.9;71.1)n = 1201	66.4(62.5;70.3)n = 979	66.5(62.1;70.8)n = 1267	68.0(65.2;70.9)n = 1267	68.3(63.0;73.6)n = 984	69.9(64.7;75.1)n = 1098			0.61(0.28;0.94)
<b>Total population</b>	<b>47.4(42.6;52.2)</b>	<b>48.6(46.3;50.9)</b>	<b>53.4(50.6;56.2)</b>	<b>52.7(49.0;56.3)</b>	<b>53.2(50.3;56.1)</b>	<b>54.0(51.0;57.0)</b>	<b>55.3(51.3;59.4)</b>	<b>57.2(55.9;58.5)</b>			<b>0.62(0.38;0.86)</b>
Missing waist circumference	112	196	206	175	238	263	257	269			

differences in the prevalence of type 2 diabetes as a function of age and abdominal obesity in 2013/2014 compared with 1999/2000, with up to 30% of the abdominally obese individuals aged ≥65 years having type 2 diabetes (30.3%; 95% CI 27.4–33.3) in 2013/2014 vs 23.8% (95% CI 18.4–29.2) in 1999/2000. The overall number of adult US residents with abdominal obesity and type 2 diabetes increased from 11.4 million in 1999/2000 to 22.9 million in 2013/2014.

We observed the same association between type 2 diabetes and obesity measured by BMI, with the prevalence of type 2 diabetes increasing significantly only in individuals aged ≥45 years with a BMI ≥30 kg/m<sup>2</sup> (Table S3). The severity of abdominal obesity also worsened over time, as demonstrated by a significant increase in the mean waist circumference in abdominally obese men and women from 1999/2000 to 2013/2014 (Table S4).

Sensitivity analyses by race/ethnicity showed similar percent increases in the prevalence of type 2 diabetes, with mean annual changes of 0.19% (95% CI 0.09–0.30), 0.27% (95% CI 0.09–0.46) and 0.19% (0.09–0.29) among non-Hispanic white, non-Hispanic black and Hispanic people, respectively. Consistent trends were also observed for the prevalence of abdominal obesity, with mean annual changes of 0.59% (95% CI 0.29–0.88), 0.74% (95% CI 0.48–1.00) and 1.10% (95% CI 0.78–1.42) among non-Hispanic white, non-Hispanic black and Hispanic people, respectively.

## 4 | DISCUSSION

This study, in which the most recent data from NHANES, including the 2013/2014 survey, were analysed, confirms that the prevalence of both type 2 diabetes and obesity have continued to increase since 1999/2000. The prevalence of abdominal obesity increased in all age groups: 20 to 44, 45 to 64, and ≥65 years; however, the increase in the prevalence of type 2 diabetes was limited to individuals with abdominal obesity, and more specifically to individuals aged ≥45 years with abdominal obesity, with no significant change in prevalence in the non-obese group and in individuals aged <45 years.

The increase in the prevalence of abdominal obesity and type 2 diabetes among the abdominally obese, combined with the aging of the population, resulted in a doubling of the number of US residents aged ≥20 years with abdominal obesity and type 2 diabetes from 1999/2000 to 2013/2014.

The present study analysed data from NHANES, which is a series of cross-sectional surveys of large representative samples of the resident non-institutionalized adult population of the USA. These surveys have been conducted consistently every 2 years since 1999 and included an interview and physical examination as well as laboratory tests that make possible a comprehensive assessment of each participant's health status.

Our operational definition for type 2 diabetes, previous diagnosis by a healthcare practitioner or HbA1c ≥6.5%, differs from other publications that analysed NHANES data, and also took into account a fasting blood glucose >125 mg/dL and a 2-hour post-load plasma glucose measurement ≥200 mg/dL.<sup>1,6,7</sup> Accordingly, our prevalence estimates for diabetes by age group are slightly lower than those recently published using data from NHANES 2011/2012 and 2013/2014.<sup>1,7</sup> We retained this definition because fasting blood

**TABLE 2** Prevalence of type 2 diabetes in the abdominally obese and non-obese populations, stratified by age group

	Prevalence, % (95% CI)										Mean change per year
	1999/2000	2001/2002	2003/2004	2005/2006	2007/2008	2009/2010	2011/2012	2013/2014	2013/2014	2013/2014	
Abdominally obese population	1935	2180	2240	2156	2866	3068	2526	2854	2854	2854	Mean change per year
20–44 years	4.7(2.6–6.8)n = 615	6.1(3.5–8.7)n = 705	5.5(3.2–7.8)n = 705	6.3(3.7–8.8)n = 751	5.0(3.4–6.5)n = 900	4.6(2.8–6.4)n = 1033	7.0(5.1–8.8)n = 895	5.8(4.2–7.5)n = 1044	5.8(4.2–7.5)n = 1044	5.8(4.2–7.5)n = 1044	0.05(–0.09 to 0.20)
45–64 years	16.0(13.0–19.0)n = 693	14.1(11.0–17.2)n = 820	17.4(14.5–20.4)n = 784	16.9(13.5–20.3)n = 769	20.2(17.1–23.4)n = 1120	18.0(15.4–20.5)n = 1179	18.1(14.1–22.0)n = 1014	20.1(17.2–23.0)n = 1066	20.1(17.2–23.0)n = 1066	20.1(17.2–23.0)n = 1066	0.31(0.09–0.54)
≥65 years	23.8(18.4–29.2)n = 627	22.7(19.9–25.5)n = 655	26.3(19.6–32.9)n = 621	25.5(21.8–29.2)n = 772	28.2(24.0–32.4)n = 846	30.0(26.0–34.1)n = 856	27.0(23.4–30.6)n = 617	30.3(27.4–33.3)n = 744	30.3(27.4–33.3)n = 744	30.3(27.4–33.3)n = 744	0.48(0.18–0.78)
<b>Total population</b>	<b>13.9(11.6–16.2)</b>	<b>13.4(11.5–15.3)</b>	<b>15.2(13.1–17.3)</b>	<b>15.0(12.9–17.2)</b>	<b>16.5(14.4–18.6)</b>	<b>16.0(14.6–17.4)</b>	<b>16.1(13.5–18.6)</b>	<b>16.9(15.6–18.2)</b>	<b>16.9(15.6–18.2)</b>	<b>16.9(15.6–18.2)</b>	<b>0.22(0.08–0.36)</b>
Non-obese population	1912	2116	1870	1858	2196	2353	2183	2205	2205	2205	Mean change per year
20–44 years	0.8(0.1–1.4)n = 967	1.8(0.9–2.6)n = 1130	0.8(0.4–1.3)n = 985	1.0(0.3–1.8)n = 990	0.9(0.4–1.5)n = 1117	0.8(0.3–1.2)n = 1265	0.6(0.2–1.1)n = 1169	0.7(0.3–1.2)n = 1149	0.7(0.3–1.2)n = 1149	0.7(0.3–1.2)n = 1149	–0.04(–0.8 to 0.1)
45–64 years	6.2(3.3–9.2)n = 507	7.6(4.2–11.1)n = 558	5.7(2.5–8.9)n = 456	6.8(3.2–10.4)n = 510	5.0(3.0–7.0)n = 658	4.6(2.3–6.9)n = 677	7.2(4.7–9.7)n = 647	6.3(4.5–8.2)n = 702	6.3(4.5–8.2)n = 702	6.3(4.5–8.2)n = 702	–0.04(–0.23 to 0.14)
≥65 years	9.1(5.5–12.6)n = 438	12.5(6.3–18.7)n = 428	13.9(10.9–16.9)n = 429	9.7(4.6–14.7)n = 358	16.4(10.7–22.0)n = 421	15.9(11.8–20.0)n = 421	12.1(7.0–17.2)n = 367	12.5(8.9–16.1)n = 354	12.5(8.9–16.1)n = 354	12.5(8.9–16.1)n = 354	0.23(–0.08 to 0.54)
<b>Total population</b>	<b>3.7(2.2–5.1)</b>	<b>5.0(3.3–6.7)</b>	<b>4.0(3.0–5.1)</b>	<b>4.0(3.0–5.0)</b>	<b>4.2(3.1–5.3)</b>	<b>3.9(2.7–5.1)</b>	<b>4.1(3.0–5.2)</b>	<b>4.0(3.2–4.8)</b>	<b>4.0(3.2–4.8)</b>	<b>4.0(3.2–4.8)</b>	<b>0.00(–0.09 to 0.09)</b>

glucose was documented in only 44% of the participants aged ≥20 years in NHANES 2013/2014 (2574 of 5769) while HbA1c was documented in >85% of the participants in each NHANES survey, with the proportion of missing data decreasing over time (7% in 2013/2014). The proportion of NHANES participants with missing HbA1c was also not significantly associated with a prior diagnosis of diabetes. In addition, HbA1c was determined from blood samples in a consistent manner throughout the present study period; therefore, we considered that an operational definition based on a previous diagnosis by a healthcare practitioner or HbA1c not only increased the power of the analysis vs a more complex definition that included fasting blood glucose, but was also unbiased across the different surveys.

We retained obesity as measured by waist circumference rather than by BMI because abdominal obesity has been described as a stronger independent predictor, not only of cardiovascular events<sup>8</sup> and mortality,<sup>9</sup> but also of type 2 diabetes<sup>5,10</sup>; however, we observed the same association between type 2 diabetes and obesity measured by BMI, with the prevalence of type 2 diabetes increasing significantly only in individuals aged ≥45 years with a BMI ≥30 kg/m<sup>2</sup>. More specific waist circumference cut-off points for the definition of abdominal obesity have been recently suggested as a function of race/ethnicity with lower thresholds among the South-Asian, Chinese and Japanese racial/ethnic groups<sup>11</sup>; however, we retained cut-off points independent of race/ethnicity, in particular, because NHANES did not identify participants in the Asian ethnic groups until 2011/2012.

As the data were collected from cross-sectional surveys in independent populations sampled every 2 years, we cannot interpret our findings as direct evidence of a causal relationship between obesity and type 2 diabetes. Nevertheless, the results are consistent with those from longitudinal studies that have pointed to obesity and, in particular, abdominal obesity, as a risk factor for type 2 diabetes.<sup>5,12,13</sup> Furthermore, our finding that the increase in the prevalence of type 2 diabetes is restricted to individuals aged ≥45 years, while the increase in prevalence of abdominal obesity affects all age groups, is consistent with the hypothesis that diabetes may result from the cumulative burden of obesity over time. From this perspective, the continuous increase in the prevalence of abdominal obesity that is observed in all age groups, and, in particular, in individuals aged 20 to 44 years, is concerning because it suggests the prevalence of type 2 diabetes should keep increasing in the next few years.

There is a trend towards an increase in the prevalence of type 2 diabetes in non-obese individuals aged ≥65 years, with a mean increase per year of 0.23% (95% CI –0.08 to 0.54). This trend remains non-significant ( $P = .15$ ), perhaps because our study was underpowered, although a total of 3206 non-obese individuals aged ≥65 years were retained for analysis.

The absence of any significant increase in the prevalence of type 2 diabetes in all participants aged 20 to 44 years also needs to be interpreted with caution as other studies have found a significant increase among young adults, not only in type 1 but also in type 2 diabetes.<sup>14,15</sup>

The stable prevalence of type 2 diabetes among individuals without abdominal obesity suggests minimal exposure to changing lifestyle risk factors among this group. Conversely, the increasing prevalence of type 2 diabetes in the obese population can be partly

explained by more severe obesity over time, as demonstrated by an increase in the mean waist circumference in abdominally obese men and women between 1999/2000 and 2013/2014. However, other factors may have played a role, such as the development of abdominal obesity at an earlier age, as demonstrated by the increase in the prevalence of abdominal obesity among those aged 20 to 44 years, or other factors associated with obesity and diabetes such as dyslipidemia, hypertension, chronic inflammation, diet, physical exercise, and smoking status, which were not analysed in this study.

Growing disparities in the risk of type 2 diabetes have been observed not only as a function of abdominal obesity and age but also geographically, with widening differences in the prevalence of diabetes among US counties from 2004 and 2012.<sup>16</sup> These disparities highlight the cumulative effect of risk factors in fragile populations and reinforce the rationale for focused primary prevention programmes.

In conclusion, the present findings highlight the critical importance of abdominal obesity, both as a key contributor to the continuing epidemic of type 2 diabetes in the USA, and as a high-priority target for potential public health interventions. The burden of type 2 diabetes can be controlled, in part, by better management of its complications. Although some progress has been made in this direction,<sup>17</sup> these results are achieved at a high financial cost. The burden of type 2 diabetes could also be controlled by primary prevention efforts and public health interventions that target modifiable risk factors: this study supports the prioritization of these efforts in the population with abdominal obesity.

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## Conflict of interest

H.C., N.H., and P.F. are employees and stockholders of AstraZeneca. S.J. has nothing to disclose. J.J.S. was employed by AstraZeneca at the time the work was conducted. M.K. received research grants from AstraZeneca, Genentech, Gilead Sciences, and Sanofi, and has served as a consultant for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Glytec, Merck (Diabetes), Novo Nordisk, Sanofi, and Takeda. John J Sheehan is an employee of Janssen.

## Author contributions

H.C. conducted the statistical analysis, contributed to data interpretation, provided critical review, and edited and approved the manuscript. S.J., N.H., P.F., J.J.S., and K.M. contributed to data interpretation, provided critical review, and approved the manuscript. H.C. had full access to all of the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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