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ORIGINAL SCIENTIFIC REPORT

Trends in Appendicitis Among Pregnant Women, the Risk for Cardiac Arrest, and Maternal–Fetal Mortality

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Abstract

Background Appendicitis is the most common extra-uterine surgical emergency requiring immediate intervention during pregnancy. However, risks for mortality and morbidity among pregnant women with appendicitis remain poorly understood. This study was conducted to determine the temporal trends of appendicitis in pregnant women, and to calculate the risk of maternal–fetal mortality and near-miss marker (i.e., cardiac arrest) among pregnant women in general, and by race/ethnicity.

Methods We conducted this retrospective study using data from the Nationwide Inpatient Sample (NIS) from January 1, 2002, through December 31, 2015. Joinpoint regression was used to estimate and describe temporal changes in the rates of all and acute appendicitis during the 14-year study period. We also estimated the risk of cardiac arrest, maternal, and fetal mortality among mothers of various racial/ethnic groups with a diagnosis of acute appendicitis. Within each group, patients without acute appendicitis were the referent category.

Results and conclusions Out of the 58 million pregnancy hospitalizations during the study period, 63,145 cases (10.74 per 10,000 hospitalizations) were for acute appendicitis. There was a 5% decline (95% CI: − 5.1, − 5.0) in the rate of appendicitis hospitalizations over the period of the study. After adjusting for covariates, pregnant mothers with acute appendicitis had increased likelihood when compared to those without acute appendicitis to suffer fetal loss (OR: 2.05, 95% CI: 1.85–2.28) and nearly fivefold increase for inpatient maternal death. In conclusion, appendicitis during pregnancy remains an important cause of in-hospital maternal–fetal mortality overall and regardless of race/ethnicity.

Introduction

Appendicitis is one of the most common causes of abdominal pain and occurs in 7% of the US population [1]. Although the causes appear multi-factorial but are not always clear, appendicitis may result from blockage to the opening of the appendix, abdominal trauma, or enlarged tissue within the wall of the appendix. It has been speculated that the disease has both genetic and environmental components, though the actual contributions of each remains poorly understood [2, 3]. Studies have shown that women have a higher risk of appendicitis misdiagnosis, higher lifetime risk of appendectomy (23% in females vs

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12% in males) and a higher frequency of post-operative complications like iatrogenic perforations [4–6].

Acute appendicitis is the most common abdominal emergency during pregnancy [7]. The resulting symptoms are difficult to diagnose for several reasons: the use of computerized tomography is contraindicated in early pregnancy as a result of radiation exposure to fetus, physiological leukocytosis is persistent during pregnancy, ultrasound imaging can provide inconclusive results and clinical signs like rebounding and guarding are often absent [8–10]. Maternal appendicitis occurs in 0.05–0.1%, or 1 in 1400–1500 births [11]. Although the hormones produced during pregnancy are believed to be a protective factor against appendicitis, the hormonal and anatomical changes associated with pregnancy further complicate diagnosis [12].

Acute appendicitis too often is misdiagnosed or diagnosed late in pregnant patients because the presentation of symptoms may not line up with the classic clinical signs of appendicitis in non-pregnant women. There are several negative health outcomes associated with appendicitis during pregnancy including: preterm delivery, septic shock, peritonitis, and maternal and neonatal morbidity. Additional complications of acute appendicitis include fetal low birth weight, pneumonia, and spontaneous abortions [10, 11]. However, there is a lack of data related to updated estimates for the association between appendicitis and maternal–fetal mortality among pregnant women in the USA [10, 13]. The aim of this paper is twofold: (1) To describe temporal trends of appendicitis in the occurrence of appendicitis among pregnancy-related admissions in the USA over the previous decades (2002–2015), and (2) to determine the association between appendicitis and maternal–fetal mortality as well as a potent near-miss marker, namely, cardiac arrest.

Materials and methods

We conducted a retrospective, cross-sectional analysis of data from the Nationwide Inpatient Sample (NIS) for the study period of January 1, 2002, to September 30, 2015. The NIS database was developed for the Healthcare Cost and Utilization project (HCUP). It is the most robust, publicly available all-payer database of inpatient hospitalization within the USA [14]. NIS utilized International Classification of Disease, Ninth revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes prior to October 1, 2015, and ICD 10-CM/PCS after that. Therefore, we restricted our study to the ICD-9-CM period. Due to the use of de-identified, publicly available data, the Institutional Review Board (IRB) of Baylor College of Medicine deemed this study as exempt.

Using bivariate analysis, we studied the relationship between various patient sociodemographic and hospital characteristics versus the prevalence of appendicitis and acute appendicitis among pregnant women in the USA. Our study population included inpatient hospitalizations among pregnant adolescent and adult women, aged 15–49 years. Appendicitis cases were defined as all non-acute and acute appendicitis-related hospitalizations; acute appendicitis cases including hospitalizations with generalized peritonitis, cases with or without peritoneal abscess and those undergoing appendectomy, whereas non-acute appendicitis included hospitalizations related to drainage of appendiceal abscess, appendicostomy, closure of appendiceal fistula, and 'other operations on appendix.' Pregnancy hospitalizations were captured using NEOMAT variable in NIS which used any maternal and/or neonatal code present in the particular hospitalization file. To identify cases of appendicitis, we scanned discharge records for ICD-9-CM diagnosis codes beginning with '540', '541' or '542' and procedure codes beginning with '47.0', '47.1', '47.2' or '47.9' (diagnosis codes beginning with '540' and procedure codes beginning with '47.0' or '47.1' were specific to identifying cases of acute appendicitis). We also used ICD-9-CM diagnosis and procedure codes to identify outcomes of interest: cardiac arrest (diagnosis codes beginning with'42.75' and procedure codes '99.60','99.63' or codes beginning with '37.91') and fetal loss (diagnosis codes beginning with '656.41', 'V27.1', 'V27.3', 'V27.4', 'V27.6', '631', '634' and '638'). Information on in-hospital death was obtained from a variable called 'DIED' in the NIS.

Next, we created joinpoint regression models to examine temporal trends in the rates of appendicitis and acute appendicitis over the study period. Joinpoint regression is a modeling technique used to analyze the varying trends of outcome over time. The joinpoint model first fits the annual rate data to a straight line (or line with zero "joinpoints"). It then iteratively adds singular increments of joinpoints, while assessing and trying to improve the performance of the model using Monte Carlo simulation technique [15]. The final model with the optimal number of joinpoints to best explain the trends over time was used to estimate the annual percentage change (APC) for each changing trend over the study period and average annual percentage change (AAPC) for the entire study period.

Given the similarity in the trends and prevalence of appendicitis and acute appendicitis for the entire study period, further analyses were run only on the primary exposure of interest, namely acute appendicitis. We calculated the prevalence of each of the outcomes (maternal death, cardiac arrest and fetal loss) among pregnant women with acute appendicitis, stratified by race/ethnicity. Unadjusted and adjusted survey logistic regression models were run to assess the association between acute appendicitis and each of our outcome variables. We also created similar models separately for Non-Hispanic (NH)-White, NH-Black, and Hispanics patients to examine the potential role of race/ethnicity in acute appendicitis among patients with each of the outcomes. The models were adjusted for patient-level characteristics including age, income, primary payer, discharge status, and hospital-level characteristics such as teaching status, bed size, and US Census region. All statistical analyses were performed using R (version 3•5•1), RStudio (Version 1•1•423), and Joinpoint Regression Program 4.6.0.0 (National Cancer Institute, Bethesda, MD). All tests of hypotheses were two-tailed with a type 1 error rate set at 5%.

Results and discussion

Results

During the study period from January 1, 2002, through December 31, 2015, there were more than 58 million inpatient hospitalizations among pregnant women. We identified 64,408 cases of appendicitis corresponding to a prevalence of 10.96 per 10,000 hospitalizations. Out of these, 63,145 cases (10.74 per 10,000 hospitalizations) were for acute appendicitis. Sociodemographic characteristics of patients with versus without appendicitis are presented in Table 1. Our analysis revealed the prevalence of appendicitis and acute appendicitis to be similar in this population during the study period. The majority of cases, approximately 88%, were among women aged 15–34 years. The highest age-based prevalence of acute appendicitis was 12.9 per 10,000 hospitalizations observed among patients in the 15–24 age category. NH-Black women had the lowest prevalence, with 7.4 cases of acute appendicitis per 10,000 hospitalizations. NH-Whites and Hispanic patients had slightly higher rates with 11.6 and 11.3 per 10,000 hospitalizations, respectively.

An overwhelming majority of patients with acute appendicitis (about 96.3%) were routinely discharged while the maternal mortality rate among patients with acute appendicitis was 0.1% (or 1 death per 1000). It should be noted that among all maternal in-hospital deaths, 52.2 per 10,000 had acute appendicitis and pregnant women in the highest zip code income stratum tended to have the lowest prevalence of acute appendicitis.

Among patients with acute appendicitis, most were privately insured (47.7%) or had Medicaid (41.9%). Mothers that were self-paying for in-hospital services had the highest prevalence of acute appendicitis at 16.1 per 10,000. Apportioning acute appendicitis cases by region revealed that the Southern part of the USA accounted for the greatest share of cases of acute appendicitis during pregnancy (35.1% of all cases) followed by the West at 26.6%. However, the South experienced the lowest prevalence of acute appendicitis in pregnancy while the West had the highest prevalence (9.7 vs 12.6 per 10,000). The prevalence of acute appendicitis cases was highest in small hospitals (11.1 per 10,000 hospitalizations), and in rural areas (12.6 per 10,000 hospitalizations).

Temporal trends in the rates of appendicitis for the 13-year study period are displayed in Fig. 1. There was a moderate annual decrease of 2.3% (95%CI: − 2.3, − 2.2) in the rate of all appendicitis. After 2011, there was a steep drop in the number of cases of all and acute appendicitis. Both all and acute appendicitis rates exhibited a 10.6 annual percent decrease from 2011 to the year 2015. Overall from 2002 to 2015, the AAPC showed a 5% decrease (95%CI: − 5.1, − 5.0) in rates of hospitalizations for acute appendicitis.

The incidence of cardiac arrest among all pregnant women with acute appendicitis was 0.2%, whereas among Hispanics, it was about sixfold at 1.1% (Table 2). Fetal loss was observed to be equally frequent (0.2%) among mothers across racial/ethnic groups. Inpatient maternal mortality associated with appendicitis was highest among Hispanic mothers (1.7%), followed by NH-Whites (0.4%) and NH-Blacks (0.2%). After adjusting for covariates, pregnant mothers with acute appendicitis were twice as likely as those without acute appendicitis to suffer fetal loss (OR: 2.05, 95% CI: 1.85–2.28). Compared to pregnant women without a diagnosis of acute appendicitis, there was a statistically significant and nearly fivefold increase for inpatient death among those diagnosed with acute appendicitis. We found NH-Whites with acute appendicitis to be about twice as likely as NH-Whites without the diagnosis, to experience fetal loss (OR = 1.89; 95% CI: 1.58–2.26*)*, and about four times as likely (OR = 4.04; 95% CI: 1.23–8.63) to experience inpatient death. Among NH-Blacks, a diagnosis of acute appendicitis was associated with approximately threefold (OR = 2.68; 95% CI: 2.12–3.38) increased likelihood of experiencing fetal loss and more than fourfold (OR: 4.42, 95% CI: 2.91–6.63) increase in maternal death, compared to NH-Blacks without acute appendicitis. Among the Hispanic population, in comparison with those without acute appendicitis, mothers with a diagnosis of acute appendicitis had elevated risk for fetal loss (OR: 1.54, 95% CI: 1.21–1.97) and maternal death (OR: 3.62, 95% CI: 1.21–9.23). Unadjusted, Hispanic mothers with acute appendicitis were more likely to experience cardiac arrest as compared to those without the diagnosis (OR: 4.76, 95% CI: 3.44–5.68) but after accounting for the effects of potential confounders, the association model did not achieve statistical significance.

Table 1 Sociodemographic characteristics of pregnant women with appendicitis and acute appendicitis

Total	Total	All appendicitis		Acute appendicitis	
	58,784,013	100% (%)	Prevalence[a]	100% (%)	Prevalence[a]
Age					
15–24 years	19,785,950	40.7	13.2	40.7	12.9
25–34 years	30,366,510	47.4	10.0	47.5	9.8
35–49 years	8,631,553	11.9	8.9	11.9	8.6
Race					
NH-White	24,995,486	46.1	11.9	46.2	11.6
NH-Black	7,141,952	8.5	7.7	8.5	7.4
Hispanic	10,801,987	19.5	11.6	19.4	11.3
Other	5,039,455	6.5	8.3	6.4	8.0
Missing	10,805,132	19.4	11.6	19.5	11.4
Discharge status					
Routine	57,013,370	96.0	10.8	96.3	10.6
Transfer	320,840	1.4	28.1	1.1	22.5
Died	7276	0.1	52.2	0.1	52.2
DAMA	161,993	0.3	12.3	0.3	10.1
Other	1,268,275	2.2	11.2	2.2	11.0
Missing	12,260	0.0	10.6	0.0	10.6
Zip income quartile					
Lowest quartile	11,376,356	18.3	10.4	18.2	10.1
2nd quartile	10,173,952	16.5	10.5	16.5	10.2
3rd quartile	9,677,929	15.5	10.3	15.5	10.0
Highest quartile	8,706,296	13.0	9.6	12.9	9.3
Missing	18,849,479	36.7	12.5	36.9	12.3
Primary payer					
Medicare	406,043	0.8	12.1	0.7	11.6
Medicaid	24,865,445	42.0	10.9	41.9	10.6
Private insurance	29,690,053	47.5	10.3	47.7	10.1
Self-pay	3,725,907	9.6	16.5	9.5	16.1
Other/missing	96,566	0.2	10.3	0.2	10.2
Hospital region					
Northeast	9,854,338	16.1	10.6	16.1	10.3
Midwest	12,825,231	22.1	11.1	22.2	10.9
South	22,857,251	35.2	9.9	35.1	9.7
West	13,247,192	26.6	12.9	26.6	12.6
Hospital bed size					
Small	6,886,766	12.2	11.4	12.1	11.1
Medium	15,879,474	26.8	10.9	26.8	10.6
Large	35,773,736	60.6	10.9	60.7	10.7
Missing	244,036	0.4	9.6	0.3	9.0
Hospital location and teaching status					
Rural	6,651,379	13.4	13.0	13.3	12.6
Urban non-teaching	22,934,580	39.8	11.2	39.9	10.9
Urban teaching	28,954,019	46.4	10.3	46.4	10.1
Missing	244,036	0.4	9.6	0.3	9.0

[a]Prevalence rate is per 10,000 maternal hospitalizations

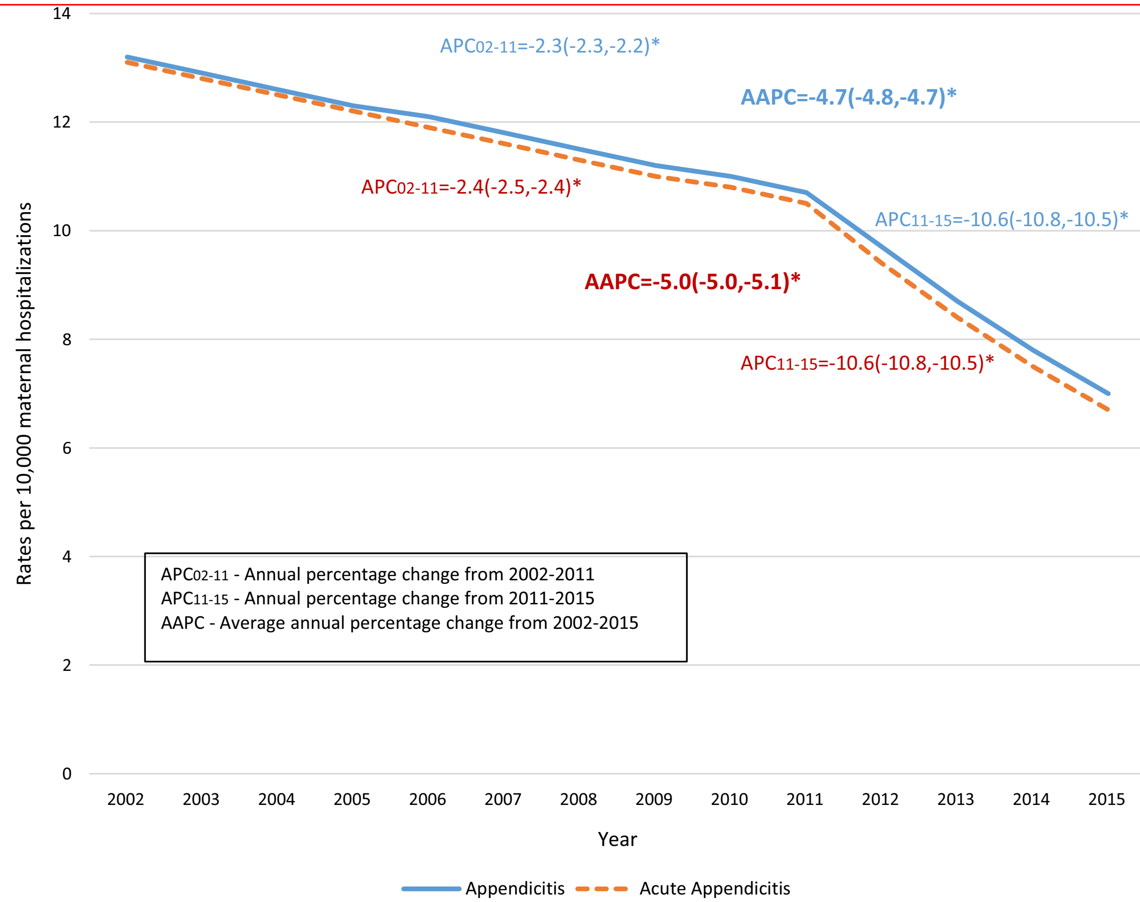

Fig. 1 Trends in rates of all appendicitis and acute appendicitis per 10,000 maternal hospitalizations (2002–2015)

Discussion

Our analysis of over 58 million maternal hospitalizations demonstrated that although there was a 5% average annual decrease in the rates of appendicitis between 2002 and 2015, most of the maternal appendicitis hospitalizations in the USA during the study period were due to acute appendicitis. We speculate that the steep decline in the rates of overall and acute appendicitis after 2011 may have resulted from policy changes in the appendicitis management but the exact reason remains unexplained. We observed an inverse dose–response relationship between maternal age and prevalence of appendicitis. Also, the majority of pregnant women with a diagnosis of appendicitis belonged to the lowest-income stratum. Additionally, the increased adjusted odds of death observed for pregnant women with acute appendicitis as compared to those without the disease indicates the potential for lethal complications among women facing both pregnancy and appendicitis, including perforated appendix, laceration of uterus during surgical intervention and post-surgical infections [16, 17].

Our analyses revealed several notable racial/ethnic disparities in maternal death and fetal loss outcomes. The adjusted odds for fetal loss increased significantly for NH-Blacks with acute appendicitis, as they were about three times as likely to experience fetal death compared to NH-Blacks without the disease. This trend echoed the current statistics in regard to Black fetal mortality [18]. Further, even though only 8.5% of the study population were NH-Black, the likelihood of maternal death was higher within this racial/ethnic group compared to NH-Whites and Hispanics (OR: 4.42 vs 4.04 vs 3.62, respectively). This greater susceptibility to mortality among hospitalized NH-Black could be explained by underlying pre-existing conditions such as uncontrolled diabetes, hypertension, and cardiac conditions [19] since Blacks with such co-morbidities tend to experience accelerated death in the presence of an acute life-threatening conditions as recently shown by the Covid-19 pandemic [20]. It is also likely that the combined synergistic effect of adverse social determinants of health (which are more prevalent among Blacks) and pre-existing comorbidities could amplify the risk of maternal mortality [21].

Table 2 Unadjusted and adjusted survey binomial regression model to assess the association between acute appendicitis and the occurrence of cardiac arrest, fetal loss, and in-hospital death—overall and among racial/ethnic groups

Acute appendicitis					
	Incidence[a]	Unadjusted model		Adjusted model[b]	
		OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Overall					
Maternal cardiac arrest	0.2%	0.61 (0.23–2.53)	0.29	0.64 (0.15–2.76)	0.55
Maternal death	0.5%	4.93 (2.45–9.90)	< 0.0001	5.23 (2.43, 10.21)	< 0.0001
Fetal death	0.2%	2.03 (1.83–2.25)	< 0.0001	2.05 (1.85–2.28)	< 0.0001
NH-Whites					
Maternal Cardiac arrest	0.0%	–	–	–	–
Maternal death	0.4%	3.52 (1.03–7.26)	0.04	4.04 (1.23–8.63)	< 0.0001
Fetal death	0.2%	1.95 (1.63–2.32)	< 0.0001	1.89 (1.58–2.26)	< 0.0001
NH-Blacks					
Maternal Cardiac arrest	0.0%	–	–	–	–
Maternal death	0.2%	3.04 (0.42–9.16)	0.27	4.42 (2.91–6.63)	< 0.0001
Fetal death	0.2%	2.77 (2.20–3.48)	< 0.0001	2.68 (2.12–3.38)	< 0.0001
Hispanics					
Maternal cardiac arrest	1.1%	4.76 (3.44–5.68)	< 0.0001	2.50 (0.29–10.69)	0.41
Maternal death	1.7%	6.34 (2.03–12.46)	< 0.0001	3.62 (1.21–9.23)	< 0.0001
Fetal death	0.2%	1.61 (1.26–2.05)	< 0.0001	1.54 (1.21–1.97)	< 0.0001

[a]Incidence of the outcome among mothers with acute appendicitis

[b]Survey binomial regression models were adjusted for age, income, primary payer, disposition, hospital bed size, hospital region and hospital location, and teaching status

'–' represents zero cases

Referent category for the models—pregnant women without a diagnosis of appendicitis

In our study, we did not find any cases of acute appendicitis and cardiac arrest among NH-White and NH-Black women. The increased likelihood of cardiac arrest (in the unadjusted model) among Hispanic pregnant women being treated for acute appendicitis, compared to Hispanics without acute appendicitis, was another notable finding. Cardiac arrest in those with acute appendicitis could stem from several complications including negative appendectomy, complications caused by anesthesia, or surgical accidents that result in bleeding [10, 22]. Although it is unclear what may contribute toward the increased likelihood of cardiac arrest among Hispanics with versus those without appendicitis, some of the likely reasons could be restricted access to health care, delayed prenatal care, late presentation, limited accessibility to facilities which are equipped with expertise and infrastructure to attend to these emergencies etc.[22, 23]. The paucity of numbers of cardiac arrest in NH-White and NH-Black women with appendicitis hampered evaluation of racial/ethnic disparities across these groups.

There are notable strengths and limitations in our study. The large sample size and source of our data serve as major strengths. Our findings are more generalizable than similar studies as we utilized standardized datasets with input from throughout the USA over an extended period of time. Our sample is representative of the nationwide inpatient population which reduces selection bias that studies with a regional focus may be subject to. There are also few limitations. The NIS does not include data on pharmaceutical therapies administered during encounters, which may have provided added clarity to our results. Secondly, as the NIS is an administrative database, it is subject to errors in reporting ICD-9-CM diagnostic classifications or other social demographics of the patient. However, due to the meticulous data management and quality assurance of NIS, it is likely that these errors, if present, are minimal [24]. Third, circumstances surrounding the adverse outcomes of maternal–fetal mortality and cardiac arrest remained unstated in the database (i.e., during a surgical intervention, post-surgical complication). The addition of this information would have allowed for a more in-depth analysis, as well as discussion of our results in relation to clinical decision making and any need for improvement in hospital protocol to decrease these adverse events among pregnant women with appendicitis.

In summary, our findings provide a distinct account of hospitalizations, health outcomes, and trends in the rates of appendicitis among pregnant women. Although there had been a decline in the rate of acute appendicitis cases in pregnancy-related hospitalizations, we observed disparities in maternal–fetal care and the need for improved protocol to decrease the risk of morbidity and mortality among the various racial/ethnic groups. These findings may be of importance for future research on the pathogenetic mechanisms behind appendicitis during pregnancy and its potential differential impact on various racial/ethnic groups.

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Compliance with ethical standards

Conflicts of interest None of the authors have any potential conflict of interest.

Human and animal rights The IRB of Baylor College of Medicine deemed this study as exempt as the study was performed on de-identified, publicly available data.

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