Obesity, Diabetes, and the Risk of Invasive Group B Streptococcal Disease in Nonpregnant Adults in the United States

Samantha I Pitts, Johns Hopkins University
Nisa M Maruthur, Johns Hopkins University
Gayle E Langley, Centers for Disease Control and Prevention
Tracy Pondo, Centers for Disease Control and Prevention
Kathleen A Shutt, University of Pittsburgh
Rosemary Hollick, Johns Hopkins University
Stephanie J Schrag, Centers for Disease Control and Prevention
Ann Thomas, Oregon Public Health Division
Megin Nichols, New Mexico Department of Public Health
Monica Farley, Emory University

Only first 10 authors above; see publication for full author list.

Journal Title: Open Forum Infectious Diseases
Volume: Volume 5, Number 6
Publisher: Oxford University Press (OUP) | 2018-06-01, Pages 1-7
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1093/ofid/ofy030
Permanent URL: https://pid.emory.edu/ark:/25593/t0svn

Final published version: http://dx.doi.org/10.1093/ofid/ofy030

Copyright information:
© The Author(s) 2018. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Accessed June 3, 2019 11:27 AM EDT
Obesity, Diabetes, and the Risk of Invasive Group B Streptococcal Disease in Nonpregnant Adults in the United States

Samantha I. Pitts,1 Nisa M. Maruthur,1,2 Gayle E. Langley,3 Tracy Pondo,4 Kathleen A. Shutt,5 Rosemary Hollick,6 Stephanie J. Schrag,7 Ann Thomas,7 Megin Nichols,8 Monica Farley,9 James P. Watt,10 Lisa Miller,11 William Schaffner,12 Corinne Holtzman,13 and Lee H. Harrison5,6

1Division of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; 2Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, Baltimore, Maryland; 3Respiratory Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia; 4Division of Bacterial Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; 5Infectious Diseases Epidemiology Research Unit, University of Pittsburgh, Pittsburgh, Pennsylvania; 6Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; 7Oregon Public Health Division, Portland, Oregon; 8New Mexico Department of Public Health, Santa Fe, New Mexico; 9Emory University, Decatur, Georgia; 10California Department of Public Health, Richmond, California; 11University of Colorado School of Public Health, Aurora, Colorado; 12Vanderbilt University School of Medicine, Nashville, Tennessee; 13Minnesota Department of Health, St. Paul, Minnesota

Background. Rates of invasive group B Streptococcus (GBS) disease, obesity, and diabetes have increased in US adults. We hypothesized that obesity would be independently associated with an increased risk of invasive GBS disease.

Methods. We identified adults with invasive GBS disease within Active Bacterial Core surveillance during 2010–2012 and used population estimates from the Behavioral Risk Factor Surveillance System to calculate invasive GBS incidence rates. We estimated relative risks (RRs) of invasive GBS using Poisson analysis with offset denominators, with obesity categorized as class I/II (body mass index [BMI] = 30–39.9 kg/m²) and class III (BMI ≥ 40.0 kg/m²).

Results. In multivariable analysis of 4281 cases, the adjusted RRs of invasive GBS disease were increased for obesity (class I/II: RR, 1.52; 95% confidence interval [CI], 1.14–2.02; and class III: RR, 4.87; 95% CI, 3.50–6.77; reference overweight) and diabetes (RR, 6.04; 95% CI, 4.77–7.65). The adjusted RR associated with class III obesity was 3-fold among persons with diabetes (95% CI, 1.38–6.61) and nearly 9-fold among persons without diabetes (95% CI, 6.41–12.46), compared with overweight. The adjusted RRs associated with diabetes varied by age and BMI, with the highest RR in young populations without obesity. Population attributable risks of invasive GBS disease were 27.2% for obesity and 40.1% for diabetes.

Conclusions. Obesity and diabetes were associated with substantially increased risk of infection from invasive GBS. Given the population attributable risks of obesity and diabetes, interventions that reduce the prevalence of these conditions would likely reduce the burden of invasive GBS infection.

Keywords. behavioral factor surveillance system; diabetes; epidemiology; obesity; streptococcal infections.

Group B Streptococcus (GBS) is an important cause of bacterial infections among adults. The incidence of invasive GBS disease in nonpregnant adults in the United States doubled from 1990 to 2007 [1]. The rate of invasive GBS disease (9.0 cases per 100,000 population) approaches that of invasive pneumococcal disease, now that pneumococcal vaccines are widely used (10.6 cases per 100,000) [1–3]. Obesity is implicated as a risk factor for some infections, such as soft tissue infections [8]. However, the risk of invasive GBS associated with obesity in nonpregnant adults is unknown.

The aim of this study was to examine the association of obesity and diabetes with the risk of invasive GBS infection among community-dwelling, nonpregnant adults.

METHODS

Surveillance and Definition of Cases

Surveillance for invasive GBS disease was conducted through the Active Bacterial Core surveillance (ABCs) network [9]. Nine ABCs sites conducted active surveillance for invasive GBS during January 1, 2010, to December 31, 2012 in California (3 counties), Colorado (5 counties, 2011–2012), Georgia (20 counties), Maryland, Minnesota, New Mexico, New York State (15 counties, 2011–2012), Oregon (3 counties), and Tennessee (20 counties). New York State was excluded in 2010 due to the high proportion of cases missing height and weight.
Invasive GBS disease was defined as isolation of GBS from a normally sterile body site (e.g., blood) in a resident of a surveillance site. Cases were identified by active, laboratory-based surveillance with laboratory audits. We included cases of invasive GBS disease in adults aged ≥18 years with a first episode of disease who were community dwelling, defined as living in a private residence, and who were not pregnant or postpartum. For patients with more than 1 episode of invasive GBS infection, only the first episode was included. Case patients were excluded if they lived in a long-term care facility, dormitory, were incarcerated, or were homeless (Figure 1).

**Data Collection**

ABCs staff abstracted data from the medical record using a standardized case report form, including location of residence, height, weight, underlying medical conditions, pregnancy status, clinical syndrome, and death before discharge. Skin and subcutaneous tissue infection was defined as cellulitis, wound or surgical site infection, erysipelas, or gangrene. Body mass index (BMI) was calculated for patients with height and weight in the medical record. Starting in 2011, BMI was collected from the medical record and used if height and/or weight data were not available. If neither height and weight nor BMI was available, or if the BMI was ≤12 or >100, data were imputed (below). Cases whose outcomes were unknown were matched to vital statistics records to determine whether they were deceased or alive.

**Analytic Methods**

**Multiple Imputation**

We imputed missing data, including BMI, race, and sex, from all invasive bacterial pathogens under surveillance by ABCs using the multiple imputation by chained equations (MICE) algorithm, with a specified imputation model for each variable [10–12]. BMI was imputed 30 times, based on the amount of missing data, using predictive mean matching and as a continuous variable [13, 14]. Binary and categorical variables were imputed with logistic regression and multinomial logit models, respectively. Variables in the model included demographics (age category, race, ethnicity, sex), state, time (year and quarter), height, weight, BMI, organism, underlying conditions (obesity, diabetes, asthma, chronic obstructive pulmonary disease, cardiovascular disease, alcoholism, smoking status, immunosuppressive therapy, leukemia, heart failure, solid organ malignancy), clinical factors (outcome, syndrome, hospitalization), and insurance provider (Medicare, Medicaid, private, or unknown).

**Denominator Estimation**

We used weighted frequencies from the 2010 Behavioral and Risk Factor Surveillance Survey (BRFSS) to estimate the population under surveillance with chronic conditions of interest [15], including state-level data sets for 3 entire states (Maryland, Minnesota, and New Mexico) and Selected Metropolitan/Micropolitan Area Risk Trends (SMART) county data for the remaining 6 surveillance areas. BRFSS SMART data were available for all counties in California, Colorado, and Oregon, and for 4 of the 20 counties in Georgia, 1 of the 15 counties in New York, and 4 of the 20 counties in Tennessee.

In BRFSS, respondents reported diabetes status, height, and weight, from which BMI was calculated. Respondents with missing BMI were excluded from the denominator estimate (5.0%). To adjust for potential bias due to BMI self-report, we adjusted the BMI of respondents in BRFSS by a correction factor equal to the age and sex stratified ratio of the mean BMI in BRFSS and the mean measured BMI in the National Health and Nutrition Examination (NHANES) [16]. NHANES was used, as both reported and measured height and weight are collected in this nationally representative study.

**Data Analysis**

We estimated incidence rates of invasive GBS disease using ABCs cases as the numerator and weighted BRFSS population estimates as the denominator; we estimated confidence intervals using 95% confidence intervals for the weighted frequencies from BRFSS. For Poisson analysis, we divided cases of invasive GBS disease and weighted frequencies of respondents from the
Figure 1. Invasive GBS disease burden per 100,000 person-years, by BMI category (2010–2012). Of the 5616 cases of nonrecurrent invasive GBS disease, 5500 (97.9%) had known underlying conditions and were used for syndrome and fatality analyses. Of these, 4737 (86.1%) resided within a geographic area for which BRFSS population estimates were available and were used to calculate stratified rates, of which 4281 (90.4%) were used for the Poisson analysis (Figure 1). Cases who were underweight (n = 127) or a race other than black or white (n = 329) were excluded due to small numbers.

Cases residing within the geographic area for which BRFSS population estimates were available did not differ by sex, BMI, or diabetes status from those outside the area, but were more likely to be younger (>65 years: 41.4% of cases within the BRFSS geographic area vs 47.6% outside of the area, P = .005) and less likely to be white (77.6% vs 84.2%, P < .001). The proportion of the most common clinical syndromes, bacteremia without a focus and cellulitis, did not differ by geographic location; however, cases within the BRFSS surveillance area had a higher proportion of osteomyelitis (16.2% vs 10.6%, P < .001) and lower proportion of pneumonia (10.8% vs 16.8%, P < .001).

Included cases were predominantly white (73.8%) and older than age 45 years (86.7%) (Table 1). Approximately half of cases had diagnosed diabetes and/or obesity. BMI was imputed in 17.0% of cases; the distribution of cases by BMI category was similar with and without the cases with imputed BMI.

### Incidence Rates

The overall crude incidence rate of nonrecurrent invasive GBS disease was 8.72 cases per 100,000 (95% confidence interval, 7.15–10.44).

### Table 1. Characteristics of Case Patients With Invasive Group B Streptococcal Disease, Active Bacterial Core Surveillance, 2010–2012

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>No. (Total = 5500)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age,y</td>
<td>18–44</td>
<td>730</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>45–64</td>
<td>2447</td>
<td>44.5</td>
</tr>
<tr>
<td></td>
<td>65 and over</td>
<td>2323</td>
<td>42.2</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>4068.4</td>
<td>73.8</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>1107.3</td>
<td>20.1</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>334.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>3226</td>
<td>58.7</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2274</td>
<td>41.3</td>
</tr>
<tr>
<td>BMI class, kg/m²</td>
<td>Underweight (&lt;18.5)</td>
<td>1617</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>Normal (18.5–24.9)</td>
<td>11373</td>
<td>20.7</td>
</tr>
<tr>
<td></td>
<td>Overweight (25.0–29.9)</td>
<td>1326.8</td>
<td>24.1</td>
</tr>
<tr>
<td></td>
<td>class I/II (30.0–39.9)</td>
<td>1752.5</td>
<td>31.9</td>
</tr>
<tr>
<td></td>
<td>class III (≥40)</td>
<td>1121.8</td>
<td>20.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Absent</td>
<td>2690</td>
<td>48.9</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>2810</td>
<td>51.1</td>
</tr>
<tr>
<td>Clinical Syndrome</td>
<td>Bacteremia without a focus</td>
<td>1726</td>
<td>31.4</td>
</tr>
<tr>
<td></td>
<td>Cellulitis</td>
<td>1595</td>
<td>29.0</td>
</tr>
<tr>
<td></td>
<td>Osteomyelitis</td>
<td>850</td>
<td>15.4</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>619</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td>Septic arthritis</td>
<td>564</td>
<td>10.3</td>
</tr>
</tbody>
</table>

*Some counts are not whole numbers due to averaging of multiply imputed data.*
The incidence rate of invasive GBS infection was higher among persons with diabetes (54.48 cases/100 000 persons) compared with those without diabetes (4.56 cases/100 000 persons) (Table 2). Incidence rates of invasive GBS infection were highest among people with class III obesity (38.30 cases/100 000 person-years) vs overweight (5.47 cases/100 000 person-years) or normal weight (5.78 cases/100 000 person-years).

In stratified analyses by age, weight, and diabetes status, the incidence of invasive GBS was greater in people with diabetes among all age and weight categories (Table 3). Notably, incidence rates were highest among patients with diabetes and either normal weight or class III obesity, with a striking elevation among patients aged 18–44 years with diabetes and normal weight. Among people without diabetes, incidence rates were highest among people with class III obesity.

### Risk Factors for Invasive GBS Infection

In bivariate analyses, increasing age, class III obesity, and diabetes were significantly associated with an increased risk of invasive GBS disease, while no associations were identified with race or sex (Table 2). In multivariable analysis, class III obesity was associated with a 4.87-fold adjusted relative risk of invasive GBS disease, while normal weight and class I/II obesity were associated with smaller but statistically significant increases (Table 3). When an interaction between diabetes and BMI was added to the multivariable model, the adjusted relative risk of persons with class III obesity was greater among those without diabetes (relative risk [RR], 8.94) compared with those with diabetes (RR, 3.02; P_interaction < .0001) (Table 4). While there was a statistically significant interaction between race and BMI, the estimated relative risks for class I/II and class III obesity by race were similar, and this interaction was not included in the final model (Supplemental Table 1).

Diabetes was associated with a 6.04-fold increase in adjusted relative risk for invasive GBS. Consistent with the incidence rates, the relative risk of invasive GBS infection associated with diabetes varied dramatically by age (P_interaction < .0001) (Table 3), with the greatest adjusted relative risk among persons aged 18–44 years with a normal BMI. The adjusted relative risk of invasive GBS associated with diabetes (compared with no diabetes) decreased with increased BMI and age. All risk factor analyses were repeated restricting to cases with known BMI with similar results (data not shown).

The estimated population attributable risks of invasive GBS disease were 27.2% overall for class I, II, and III obesity and 40.1% for diabetes. Of the population attributable risk for obesity, 59.8% was due to class III obesity.

### Clinical Syndrome

The frequency of common clinical syndromes varied by BMI category and diabetes status. Adjusting for age, sex, race, and diabetes status, case patients with class I/II and class III obesity were more likely to have skin and subcutaneous tissue infection (SSTI) and less likely to have bacteremia without a focus (reference: overweight) (Table 5). Adjusting for age, sex, race, and BMI category, case patients with diabetes were more likely to present with osteomyelitis and SSTI and less likely to present with pneumonia and bacteremia without a focus compared with patients without diabetes. Adjusting for age, sex, BMI, and diabetes status, black patients were less likely to have SSTI and more likely to have bacteremia without a focus.

### Case Fatality

In multivariable logistic regression, adjusting for age, race, sex, diabetes, and clinical syndrome, neither class I/II nor class III obesity was associated with an increased odds of death in cases of invasive GBS (reference: overweight) (Table 5). Diabetes was associated with lower adjusted odds of death (reference: no diabetes; OR, 0.73). Black race was associated with a higher adjusted odds of death compared with white race (OR, 1.65). Of the clinical syndromes, septic shock was associated with the highest adjusted odds of death (reference: osteomyelitis; OR, 64.32), followed by pneumonia (OR, 11.53), and bacteremia without a focus (OR, 8.34).
DISCUSSION

In this study, class III obesity and diabetes were independently associated with 5-fold and 6-fold increases in adjusted relative risk of invasive GBS disease, respectively, while class I/II obesity was associated with smaller increases. People with diabetes and either normal weight or class III obesity had the highest incidence rates of invasive GBS infection. Among people without diabetes, those with class III obesity had the highest rates of invasive GBS infection. Identification of these populations at high risk for invasive group B streptococcal disease is critical to the development of effective prevention strategies as well as timely diagnosis and treatment.

Diabetes was strongly associated with clinical presentation of osteomyelitis, while obesity was associated with SSTI, including cellulitis. Cellulitis was less commonly observed among black populations, which could be due to difficulties in detecting a subtle cellulitis among dark-skinned individuals. Neither obesity nor diabetes was associated with increased risk of death among patients with invasive GBS infection; in fact, diabetes was associated with a small but statistically significant decrease in mortality. Although we adjusted for clinical syndrome in the analysis of risk of death, it is possible that this decreased risk reflects the lower mortality associated with SSTI and osteomyelitis, which were most strongly associated with diabetes and obesity.

Three previous small studies have shown a strong association between the risk of invasive GBS infection and diabetes [20–22]. In 1 study, the risk associated with diabetes was greatest among young adults and decreased with age [20], results that were confirmed in our larger study.

We found that people with diabetes and normal weight were at a higher risk than those with overweight, which was particularly striking among young adults (aged 18–44 years). The reasons for the observed increased risk among normal weight persons could be because we misclassified some individuals as having normal BMI. While the BMI of cases was abstracted from the medical record, the height used to calculate BMI is likely a self-reported measure. A systematic review comparing direct measurement vs self-report of variables for calculation of BMI found a trend toward over-reporting of height, which would result in misclassification of some persons with overweight in the normal weight category [23]. The observed increase in normal weight persons might also represent the effect of an uncontrolled confounder, such as smoking. Finally, among the young patients with diabetes and normal weight in particular, this might represent a biological difference, such as an association with type 1 diabetes. Unfortunately, we are not able to distinguish type 1 from type 2 diabetes within our data. Future studies are needed to confirm this finding and examine these potential causes.

Obesity, Diabetes, and Invasive GBS Disease • OFID • 5
Diabetes is a recognized risk factor for infections, including lower respiratory tract, skin and soft tissue, and urinary tract infections. More recent evidence also implicates obesity as a risk factor, most notably for skin and soft tissue infections, as identified in our study [24–27]. A study of otherwise healthy blood donors found that a BMI >30 was associated with a 50% increase in risk of hospitalization for infection, with an increased risk in abscesses among both sexes (hazard ratio [HR], 2.2), overall skin and subcutaneous tissue infections among men (HR, 2.3), and respiratory infections and cystitis among women (HRs, 1.6 and 2.2, respectively) [28]. Our results support the growing body of evidence that obesity is a risk factor for infections. However, the magnitude of the association is notably larger than identified in the population-based study above.

Possible mechanisms for the association between obesity and invasive GBS infection include changes in skin barrier function or alteration of immune function [29]. Obesity triggers a cascade of metabolic dysregulation that contributes to the development of type 2 diabetes [30]. These chronic inflammatory changes might also contribute to the risk of infection, including invasive GBS disease. In addition, the intestinal microbiota differs in people with normal weight vs obesity [31–33], and some studies have identified increased GBS colonization among pregnant women with diabetes and obesity [34–36]. However, the prevalence of GBS colonization among nonpregnant adults with diabetes and obesity and the contribution of colonization to our findings are unknown.

The estimated population attributable risks of invasive GBS disease were high for both diabetes (40.1%) and obesity (27.2%), which indicates that efforts to reverse the epidemic of obesity and diabetes could substantially reduce the incidence of invasive GBS infection [37, 38]. GBS vaccines are in development for prevention of neonatal disease [39, 40]. The impact of these vaccines in adults will depend in part on the immunogenicity of the vaccines in this population, which may be impacted by age and underlying conditions.

Our study is limited by the quality of the data used in our analyses. We obtained BMI and diabetes data on case patients with invasive GBS from abstraction of medical records and did not collect information on the type of diabetes or level of diabetes control (eg, serum hemoglobin A1C test). BMI was imputed using multiple imputation techniques in 17% of cases. However, our results were similar with and without the inclusion of cases with imputed data. Case patients may have undiagnosed or undocumented diabetes, which could lead to residual confounding in the association between obesity and risk of invasive GBS. However, class III obesity remained associated with invasive GBS infection among persons with diabetes. Although we used self-reported data in BRFSS for denominator estimates of the prevalence of diabetes and obesity in the surveillance population, we corrected for bias in self-report of BMI. Despite this, we may still underestimate the prevalence of obesity. Additionally, BMI is not an ideal measure of adiposity; the relationship between BMI and adiposity varies across demographic groups [41, 42]. We were unable to include ethnicity in our analyses due to missing data. We were not able to account for socioeconomic status, which may further confound the relationship between invasive GBS and diabetes and obesity. As our study focused on community-dwelling adults, our results may not be generalizable to adults living in care facilities.

In summary, obesity and diabetes were associated with a substantially increased risk of invasive GBS infection. Public health efforts that reduce the prevalence of these conditions among nonpregnant adults would likely lead to a decreased incidence of this serious infection.

**Supplementary Data**

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.
Acknowledgments

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Financial support. This work was supported by the National Institutes of Health, the Ruth L. Kirschstein National Research Service Award (T32HP10025), and the Centers for Disease Control and Prevention Emerging Infections Program.

Potential conflicts of interest. All authors have reported no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


