VASCULAR ACCESS IN CRITICALLY ILL PEDIATRIC PATIENTS WITH OBESITY

BY

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LIST OF ABBREVIATIONS

BMI	Body mass index
CI	Confidence interval
CVC	Central venous catheter
HR	Hazard ratio
IQR	Interquartile range
LOS	Length of stay
OR	Odds ratio
PICC	Peripherally-inserted central catheter
PICU	Pediatric intensive care unit
PIV	Peripheral intravenous cannula
VPS	Virtual Pediatric Systems, LLC

ABSTRACT

Background: Pediatric obesity is associated with poor outcomes for hospitalized children. Vascular access is essential in critically ill patients. Our aim was to evaluate whether critically ill patients with obesity are more likely to undergo CVC insertion and develop related complications.

Methods: We performed a retrospective cohort study within the Virtual Pediatric Systems, LLC database of critically ill patients 2-17 years old admitted between 2009 and 2014. We collected demographics, height and weight, diagnoses, type and duration of vascular access, and associated complications. Patients were categorized into normal-weight, overweight, and obese; underweight patients were excluded. We used mixed-effects multivariable logistic regression to test BMI category as an independent predictor of CVC placement.

Results: We identified 120,272 unique patient admissions. A total of 73,964 devices were placed in 45,409 patients. Most device types placed differed significantly by weight status. Subjects with class 3 obesity were less likely (OR 0.69, 95% CI 0.63-0.75) to undergo device placement compared to normal-weight subjects. Class 3 obesity was an independent risk factor for developing a complication, with odds ratio 1.51 (95% CI 1.12-2.05).

Conclusions: Severe obesity is associated with decreased likelihood of placement of a vascular device but increased likelihood of related complications.

CHAPTER ONE

Background:

Pediatric obesity remains a significant public health concern, affecting 17.0% of American youth[1] with continued rise in the rates of severe obesity.[2] Overweight and obesity have traditionally been managed in the outpatient setting; however, two recent systematic literature reviews suggest that weight status may influence hospital outcomes[3] and incidence of adverse patient safety events[4] among pediatric inpatients. Previous studies addressing these outcomes in critically ill pediatric inpatients have yielded mixed results. In a single-institution study of all pediatric intensive care unit (PICU) admissions requiring mechanical ventilation, no significant differences were seen in mortality, PICU length of stay (LOS), or number of ventilator days based on weight status.[5] However, in a larger national database study, children with obesity were found to have increased mortality when admitted to the PICU.[6] In addition, poor outcomes have been reported specifically for patients with obesity and trauma,[7] burn,[8] severe acute asthma exacerbations,[9] and pandemic H1N1 influenza A.[10] The findings in adults are also inconsistent. In one prospective single-center study of critically ill adult trauma patients, obesity was associated with an odds ratio of 7.1 (95% confidence interval (CI) 2.1-8.9) for death in the hospital.[11] However, a meta-analysis of adult critical care patients demonstrated that obesity was associated with prolonged ICU LOS and duration of mechanical ventilation but not with excess mortality.[12]

Pediatric patients with obesity may also have increased resource utilization while hospitalized, although this has not specifically been assessed in the PICU. Two studies demonstrated that children given a diagnosis code for obesity during their hospitalization for asthma, pneumonia, affective disorders, or appendicitis had significantly higher hospital charges than those without the diagnosis.[13,14] However, the diagnosis was applied to fewer than 2% of all admissions, supporting that obesity is routinely underdiagnosed in the inpatient setting[15-17] and making these results difficult to interpret. The mechanisms underlying the poor clinical outcomes and increased resource utilization of pediatric inpatients with obesity are unknown.

The Role of Vascular Access:

Vascular access is a crucial component of care in critically ill patients, allowing the delivery of medications, fluids, parenteral nutrition, and blood products. Although a peripheral intravenous cannula (PIV) is often inserted initially, central venous access may be considered to address issues with duration of access, multiple access sites, or the infusion of compounds that could be toxic to the surrounding tissues in the case of an extravasation. Obtaining central venous access requires skilled personnel, specific sterile and disposable equipment, imaging to confirm placement, and often bedside sedation or operating room access.[18] In addition, central venous access predisposes the patient to a wide variety of complications, including thrombosis, infection, bleeding, and injury to surrounding structures.[19] Requirement for central venous access therefore could be associated with poor clinical outcomes, higher incidence of adverse patient safety events, and the increased resource utilization previously noted for patients with obesity. Although anatomic considerations might suggest that patients with obesity would have an increased requirement for and increased complication rate with central venous access, this has not previously been studied in pediatric patients.

Vascular access is a very common hospital procedure, with millions of central venous access devices and even more peripheral venous access devices used.[19] The type of access required is influenced by the patient’s indication for admission, their severity of illness, and previous attempts at access.[20] Options for central access include peripherally-inserted central catheter (PICC) lines or central venous catheters (CVC), which can be tunneled or nontunneled. PICC lines are placed into a large peripheral vein, such as the basilic, cephalic, or long saphenous vein, while common sites for CVC placement include the bilateral internal jugular veins, subclavian veins, and femoral veins. Alternate sites that have also been proposed include the greater saphenous vein[21,22] and external jugular vein.[23] For either type of line, the catheter tip should be placed at the junction of the right atrium with the superior or inferior vena cava to be considered central. Tunneled CVCs, such as Broviac or Hickman catheters, require surgical placement and are used for longer-term access. Totally implantable venous access devices, also known as ports, feature a reservoir surgically implanted beneath the skin and attached to a CVC. Finally, intraosseous vascular access is an alternative now frequently used in emergency situations but not considered for long-term use.[24-26] Traditionally, nontunneled CVCs are placed for short-term use (7-10 days), PICCs are recommended for medium-term use (1 week to 6 months), and tunneled CVCs or ports are indicated for long-term use (months to years).[19]

Very little has been published about predicting the need for central venous access among critically ill patients. In one study, critically ill adult trauma patients with obesity were more likely to undergo CVC placement and to have more CVC days than their normal-weight counterparts.[11] To our knowledge, this has not been assessed in pediatric patients.

Complications of Vascular Access:

Vascular access is associated with a variety of complications, both during the acute placement and during maintenance of the line. These complications are not uncommon. In one study of pediatric admissions related to adverse medical device events, events involving a vascular access device were the most common, accounting for 26.6% of all admissions.[27] In a recent systematic review, 25% of all central lines in pediatric patients failed before therapy was completed, at a rate of 1.97 per 1000 catheter-days.[19] Adverse patient safety events associated with vascular access devices can prolong LOS and increase hospital charges; in one study, an iatrogenic pneumothorax increased LOS by a mean of 3.39 (standard error 2.11) days and increased charges by $53,604.[28] The incidence and variety of complications depends on catheter type and location, as well as patient factors.

Complications occur in 3 to 25% of acute insertions of central lines.[29-32] These can include patient issues, such as increased needle sticks, prolonged sedation, and delay of therapy, as well as anatomic issues, including arterial puncture, hemorrhage, subcutaneous emphysema, cardiac rhythm dysfunction, and nerve injury. More rare but potentially life-threatening complications include pneumothorax, hemothorax, hemomediastinum, hydromediastinum, superior vena cava syndrome, air embolism, and cardiac tamponade.[33,34] Traditionally, CVC insertion is directed by anatomic landmarks, which may be more difficult to appreciate in patients with obesity. More recently, insertion has been performed with the use of ultrasound imaging to aid in correct placement, which decreases the number of needle sticks required and the rate of complications.[34,35] Ultrasound is noted to be especially beneficial in children with soft tissue edema.[36] While its use has not been specifically studied in children with obesity, one recent survey of pediatric surgeons indicated that morbid obesity was a leading patient characteristic that would encourage them to use real-time ultrasound during CVC placement.[37]

Complications with an existing line may be infectious or non-infectious. Infections can occur at the site of the line (phlebitis or exit-site infection) or systemically (bloodstream infection or sepsis). Non-infectious complications encompass a broad range of events. Mechanical issues such as displacement, occlusion, and breaks or leaks (including extravasation of potentially cytotoxic material) are among the most common complications.[19] There is a well-established risk of thrombosis or thromboembolism in children with a CVC[19,38-41] and, more rarely, the development of a calcified cast at the site of a thrombus.[42,43] Finally, at the time of catheter removal, there is a risk of retained lines or fragments, which may require additional intervention for removal.[44-46]

Catheter type influences the rate of complications, with a pooled proportion of failure of 30.1% (95% CI 24.4-36.1%) for PICC lines and 29.2% (95% CI 15.9-44.6%) for tunneled catheters compared to 15.8% (95% CI 9.4-23.5%) for totally implanted catheters.[19] In one single-institution prospective study of PICC placement in pediatric patients, 29% of PICC lines were removed for complications, most notably displacement (8%), occlusion (7%), and suspicion of sepsis (8%). Of note, catheter-associated sepsis was only documented in 2% of PICC lines in this series.[47] Similar results were seen in another pediatric series: 37% of PICC lines experienced a complication, including displacement (9.3%), mechanical problems including obstruction (13.6%), and infectious complications (13.6%). Of these, 4.3% were identified as PICC-associated bloodstream infection, and 1.4% were identified as PICC-related bloodstream infection.[48] Another study of 369 non-tunneled CVCs placed in a single PICU demonstrated maintenance-related complications in 17.3% of catheters, with 7.5% of CVCs lost due to complications. Obstruction was the most common (7.0%) followed by accidental removal (3.8%), subcutaneous extravasation (3.8%), and central venous thrombosis (2.2%).[29]

The site of the catheter likely influences the rate of complications. PICC lines where the tip is considered central (at the junction with the right atrium) have a lower incidence of complications (3.8%) than those where the tip is noncentral (28.8%).[49] In a Cochrane review focused on adult patients, subclavian placement was associated with a lower incidence of infectious and thrombotic complications than femoral placement for short-term catheterization. No significant differences were seen between subclavian and internal jugular CVCs for long-term catheterization.[50] Anatomic variations in vein structure and location could predispose to complications. One ultrasound-based study found that the incidence of anatomic variation was different between the subclavian vein (7.4%), internal jugular vein (7.7%), and femoral vein (9.8%).[51] The authors noted that the incidence of variation at each site was different between patient age groups but did not assess if obesity also contributed to this variation.

Fewer studies have looked at patient factors contributing to vascular access complications, and the results have been highly variable. Following multivariate analysis, older patient age was significantly associated with infectious complications of PICC lines[48] but other studies have shown associations between younger age and infected CVCs.[52] Failure of insertion may be more common in younger patients, although this has not been found in every study.[40,53] Younger age was also associated with displacement in one series.[52] In a prospective study, none of the patient factors assessed (age, weight, and sex) were associated with early mechanical complications of non-tunneled CVCs.[54] The patient's diagnosis may also affect the incidence of complications. Specifically, acute lymphoblastic leukemia was associated with CVC dislocation and thrombosis while nonmalignant disease was associated with line rupture in one cohort of children affected by oncologic, hematologic, or immunologic diseases.[52] In another series, primary disease was not significantly associated with any vascular access complications.[32] Many of these studies involve relatively small sample sizes, which may explain some of the variability in results.

Difficulties with access could contribute to the poor clinical outcomes noted for pediatric inpatients with obesity, but attempts to investigate associations between obesity and CVC complications have produced inconsistent results. Obesity may complicate attempts to place CVCs,[55] PICCs,[56] and PIVs.[57] However, in one prospective study, neither body mass index (BMI) nor weight-to-age z-score was related to time to

PIV placement or success at first attempt among pediatric patients following multivariate analysis.[58] Blood vessel diameter has been found to vary with body size, [59] but it is not clear if this directly affects device placement or complication rate. Adult patients with obesity may be at risk for increased complications associated with CVCs.[60,61] Less is known about these associations in children. One prospective observational study from a children's hospital in Thailand revealed that patient BMI >30 kg/m2 was a risk factor for mechanical complications during CVC insertion, including inability to place catheter, hematoma, arterial puncture, and pneumothorax.[62] In children, obesity is calculated by comparison of BMI to age- and gender-specific reference norms, which makes the absolute cutoff used in this study difficult to interpret. In contrast, a single-center prospective study from Brazil reported that lower body weight was associated with an increased risk of failure at the first insertion site.[63] This study did not collect height to allow calculation of BMI and did not report whether associations between body weight and other catheter-related complications were assessed. Potential associations between patient age and insertion failure[53] make it more difficult to interpret these results without BMI percentiles for age and gender. Therefore, an association between pediatric obesity and complications with catheter insertion is controversial.

Very little data exists on obesity and complications with existing catheters. Some previous studies have demonstrated an increased incidence of infectious complications (broadly defined) among patients with obesity,[3] but the incidence of CVC-associated infections has not specifically been assessed. Patients with obesity are known to have a baseline increase in inflammatory markers,[64] which may contribute to the severity of many illnesses, including infections. This increased baseline inflammation is also thought to contribute to an association between obesity and pediatric thromboembolic events. This association is well-established in adults,[65] and obesity is included in adult risk assessment scores.[66] There is growing evidence to support an association with venous thromboembolic events in children, with odds ratios from 2-3. [67,68] Obesity has been proposed for inclusion in recent algorithms for thromboprophylaxis of hospitalized adolescents.[69] Therefore, obesity may potentially influence both infectious and non-infectious complications of CVCs.

Proposal and Methods:

Although anatomic and inflammatory considerations suggest that children with obesity might have an increased requirement for central access and increased rate of complications with CVCs, this has not previously been assessed. In this study, we will evaluate associations between overweight and obesity and difficulties with vascular access in critically ill pediatric patients using the Virtual Pediatric Systems, LLC (VPS) database. This database includes deidientified patient information from over 600,000 admissions to 142 member PICUs. It was originally developed for benchmarking and quality assessment.[70] Required data elements include patient demographics, primary diagnosis, severity of illness, LOS, and procedures, including CVC placement. Optional data elements that will be used in this study include height, race, and complications associated with CVC procedures. In children, overweight and obesity are determined by calculation of BMI using height and weight followed by comparison to reference norms by age and gender, with BMI <5% considered underweight, BMI 5-<85% considered normal-weight, BMI 85-<95% considered overweight and BMI >=95% considered obese.[71,72] For this study, the primary analysis will use BMI category as the exposure, which will include only those patients with height recorded. As a secondary analysis, we will include all patients using multiple imputation for missing height data to determine if this results in significant differences in our findings.

Severity of illness may significantly affect the need for vascular access, and possibly the susceptibility to complications, and will be considered a potential confounder in our analysis. The Paediatric Index of Mortality 2 (PIM2) score is commonly used to assess severity for PICU patients and is a required element in the VPS database. It includes ten variables recorded at the time of PICU admission (Table I) and demonstrated an area under the receiver operating curve of 0.9 (0.89-0.92) for discriminating between death and survival when validated in 20,787 children in Australia, New Zealand, and the United Kingdom.[73]

Table I: PIM2 Score[73]

Absolute value of (Systolic blood pressure – 120)	Elective admission (Y/N)
Pupils fixed to light (Y/N)	Recovery post procedure (Y/N)
100 x [Fraction of inspired oxygen/PaO2]	Bypass (Y/N)
Absolute value of base excess, mmol/L	High Risk diagnosis (Y/N)
Mechanical ventilation (Y/N)	Low risk diagnosis (Y/N)

PaO2: plasma concentration of oxygen, mm Hg
High risk diagnosis: cardiac arrest preceding ICU admission, severe combined immunodeficiency, leukemia or lymphoma after first induction, spontaneous cerebral hemorrhage, cardiomyopathy or myocarditis, hypoplastic left heart syndrome, HIV infection, liver failure as main reason for ICU admission, neurodegenerative disorder
Low risk diagnosis: asthma, bronchiolitis, croup, obstructive sleep apnea, diabetic ketoacidosis

The availability of multicenter deidentified patient data through the VPS database is a major strength of this research project. However, it does introduce some limitations. We will have incomplete information on patient heights and CVC complications, and there is a potential for the introduction of bias based on which centers do report this information. To minimize this, we will repeat our analysis using multiple imputation for missing data to assess the effects on our results. We will also be able to assess associations between reporting and center characteristics, such as unit size and academic designation. Without primary data review, we will not have access to information about all potential confounders, such as catheter site or use of ultrasound guidance during CVC placement. However, our findings may be useful in developing future studies with access to these specific data.

In summary, an association of pediatric overweight and obesity with poor clinical outcomes for hospitalized patients has previously been demonstrated, but discrete factors contributing to these poor outcomes have not been identified. This study will investigate a potential role for complications with vascular access using a large, nationally-representative dataset of children requiring intensive care. These results are important for clinicians who care for patients with overweight and obesity and those who counsel patients on the risks of these diseases.

Specific Aims:

Primary Aim: To test the hypothesis that critical care patients with overweight and obesity are more likely to undergo placement of a vascular access device compared to their normal-weight counterparts in a national sample of United States PICUs (VPS database).

Secondary Aims: To test the hypothesis that patients with overweight and obesity will undergo device placement earlier in their hospital admission, will have an increased number of device days, and will be more likely to experience complications related to vascular access devices.

CHAPTER TWO

Background:

Pediatric obesity continues at unacceptably high levels, with significant impact on child health and well-being.[1,2] In hospitalized children, obesity has been associated with increased mortality,[3,6] increased hospital length of stay (LOS),[3] and increased incidence of adverse patient safety events.[4] In both adult and pediatric critically-ill patients, obesity has been associated with increased risk of death.[6,11]

Vascular access is a crucial component of care in critically ill patients, allowing the delivery of medications, fluids, parenteral nutrition, and blood products. Access may be more difficult to obtain in patients with obesity due to anatomic considerations, but data are limited to predominantly single-center studies with small sample sizes and inconsistent definitions of obesity.[62,63] In addition, central venous access predisposes patients to a wide variety of complications.[19] Obesity may independently increase the risk of some of these complications, such as thrombosis[67,68] and infection.[3] It is unknown if difficulties with access contribute to the increased PICU mortality noted for children with obesity.[6]

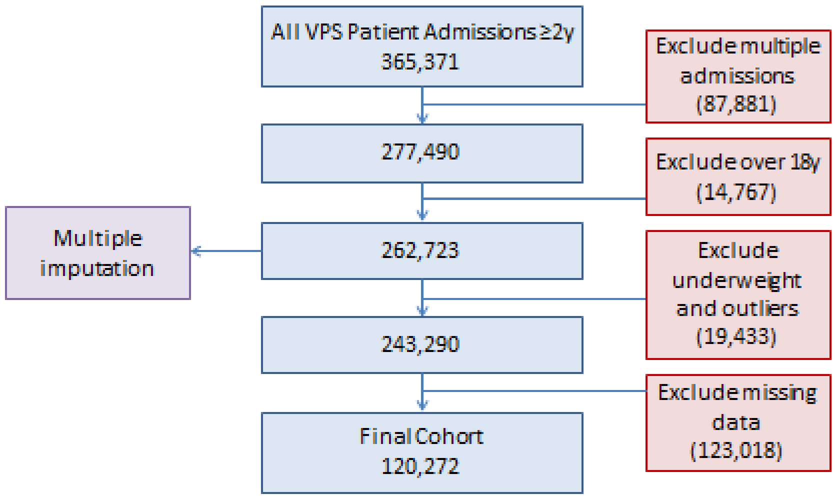
The goal of this study is to investigate associations between obesity and vascular access procedures and complications in a national sample of critically ill pediatric patients. Our hypothesis is that patients with obesity will require more vascular access procedures than their normal-weight counterparts, will require such procedures earlier during the hospitalization, and will experience more related complications.

Methods:

This was a retrospective cohort study of de-identified patient data collected from January 1, 2009 to December 31, 2014 within the Virtual Pediatric Systems, LLC (VPS) database. The database includes specified data elements that are prospectively collected by member pediatric intensive care units (PICUs) across the United States. Data were provided by VPS; no endorsement or editorial restriction of the interpretation of these data or opinions of the authors has been implied or stated. This study was determined to qualify for exemption by the Wake Forest School of Medicine institutional review board.

Patients admitted to member PICUs age 2 to <18 years were evaluated for inclusion in the analysis. Patients under 2 years of age were excluded, as overweight and obesity are not consistently defined for this age group in the United States. Patients with missing height and/or weight were excluded. Underweight patients were excluded due to a high likelihood of comorbid pathology which would confound the analysis. All other patients were included (see Figure 1). For patients with multiple admissions, only the first admission was considered in this analysis. Data elements obtained from VPS included patient demographics; clinical characteristics including diagnoses and severity of illness/risk of mortality by Pediatric Index of Mortality 2 (PIM2) score; weight; height when available; PICU admission, discharge, and LOS; outcome and disposition; and type and duration of vascular access. The risk of mortality according to the PIM2 score was chosen as a measure of severity of illness because it is a required data element in the VPS database. Based on the distribution of risk of mortality, patients were categorized as follows: 0%, 0-0.5%, 0.5-1%, >1%.

Figure 1: Cohort selection



The primary exposure was BMI category, calculated according to Center for Disease Control guidelines[72,74] from age, gender, height, and weight. Outliers (height- and weight-for-age z-scores <-5 or >5) were excluded from the analysis. BMI percentile was used to classify subjects as follows: 5% - <85% normal-weight, 85% - <95% overweight, and ≥95% obese.

The primary outcome was placement of any vascular device. Vascular devices were categorized as arterial catheters, percutaneous CVCs, peripherally inserted central catheters (PICCs), Port-a-caths, Broviac/Hickman catheters, and hemodialysis catheters; peripheral intravenous catheters (PIVs) were not included. The clinical indication for arterial lines, hemodialysis catheters, and Port-a-caths may be diagnosis-specific and different from the indications for the other devices studied. Therefore, as a secondary analysis, we evaluated placement of any venous rescue device (percutaneous CVC, PICC, and Broviac) as an outcome as well as placement of each of these devices individually as outcomes. We determined device time in the PICU and total device time, with time data censored if the device was present on admission or at discharge from PICU. For those devices placed in the PICU, we determined the timing of placement following admission.

Complications are not a required field; however, centers that committed to reporting these data did so consistently. Complications with vascular access were organized into categories as follows: Mechanical (Broken device, Displaced/dislodged, Not Working not otherwise specified, Obstructed) Infection (Device related Blood Stream Infection, Non Surgical Site Infections, Surgical site infection – Deep, Surgical site infection – Superficial), Thrombosis (Clotted/thrombosed), Bleeding (Bleeding requiring reoperation, Bleeding not requiring reoperation), and Other (Brain herniation, Bronchopleural fistula, Cardiorespiratory arrest, Death, Dysrhythmia, Hemothorax, Hypotension, New Onset Seizure, Other, Paresis/Paralysis, Pleural effusion requiring drainage, Pneumothorax, Reoperation during admission (unplanned)).

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC). Descriptive statistics of admission characteristics were compared by weight status using Pearson chi-square analysis for categorical variables and ANOVA for continuous variables. Univariate analyses were performed to identify factors associated with our outcomes, including BMI category, age, sex, severity of illness score (PIM2), and post-operative status. Factors found to be significantly associated with device placement in the univariate analysis were included in a mixed-effects multivariable logistic regression model; a mixed-effects model was chosen to account for correlation within each unit. Each admission was only represented once in the clinical and demographic information and in the logistic regression modeling. In contrast, data on device time were determined as the median per device, so an admission could be represented more than once. We generated Kaplan-Meier estimates of median total device time by BMI category and used Cox proportional hazard modeling to identify factors associated with total device time. A p value of <0.05 was used to define statistical significance.

Results:

We identified 120,272 unique patient admissions meeting all inclusion criteria to 94 PICUs within the United States. These patients were 63% normal-weight, 16% overweight, and 21% obese, with other demographics displayed by BMI category in Table II. Patients with obesity were more likely to be male and Black or Hispanic (p<0.001). They were more likely to have an unscheduled PICU admission (p<0.001), and severity of illness (expressed as percent risk of mortality) increased with increasing weight category.

Table II: Patient and device placement characteristics by weight category

	Normal-Weight (N=75,995)	Overweight (N=18,854)	Obese (N=25,423)	P value
Age – N(%)				
2-5 years	25,254 (33%)	5278 (28%)	7659 (30%)	
6-12 years	25,497 (34%)	6765 (36%)	9280 (37%)	<0.001
13-18 years	25,244 (33%)	6811 (36%)	8484 (33%)	
Male – N(%)	40,626 (53%)	9886 (52%)	14,648 (58%)	<0.001
Race/Ethnicity – N(%)				
White	38,877 (55%)	9215 (52%)	11,254 (47%)	
Black	13,718 (19%)	3641 (21%)	5577 (23%)	<0.001
Hispanic	10,317 (15%)	2914 (17%)	4455 (19%)	
Other	7841 (11%)	1854 (10%)	2543 (11%)	
Unscheduled Admission – N(%)	53,171 (70%)	13,975 (74%)	19,119 (75%)	<0.001
Post-Operative Patient – N(%)	28,230 (37%)	6319 (34%)	8480 (33%)	<0.001
Trauma Patient – N(%)	8445 (11%)	2277 (12%)	2530 (10%)	<0.001
PIM-2 risk of mortality – Mean % (SD)	1.77 (7.49)	1.91 (8.11)	1.96 (8.46)	0.001
PICU LOS (days) – Median (IQR)	1.26 (0.86-2.59)	1.30 (0.85-2.69)	1.40 (0.87-2.84)	<0.001
Vascular Access Placed				
Any Device	29,491 (39%)	6856 (36%)	9062 (36%)	<0.001
Rescue CVC	17,419 (23%)	3982 (21%)	5422 (21%)	<0.001
Device Type				
Arterial catheter	22,888 (30%)	5139 (27%)	6562 (26%)	<0.001
Percutaneous CVC	12,458 (16%)	2705 (14%)	3560 (14%)	<0.001
PICC	5330 (7%)	1399 (7%)	2098 (8%)	<0.001
Portacath	1840 (2%)	454 (2%)	621 (2%)	0.97
Hemodialysis	1266 (2%)	384 (2%)	534 (2%)	<0.001
Broviac/Hickman	1163 (2%)	304 (2%)	395 (2%)	0.71
Device Placement				
Present on Admission	21,335 (38%)	4680 (25%)	5821 (23%)	<0.001
Present at Discharge	11,212 (15%)	2808 (15%)	3971 (16%)	0.004

* Race/ethnicity data were missing for 8066 subjects (5242 normal-weight, 1230 overweight, 1594 obese).

A total of 73,964 devices were placed in 45,409 patients (37.8% of the total cohort). Arterial catheters and percutaneous CVCs were placed the most commonly. Most device types placed differed significantly by weight status, with relatively more PICC lines and fewer arterial lines and percutaneous CVCs placed in patients with obesity, as shown in Table II. The percentage of patients who underwent placement of any vascular access device (p<0.001) or any venous rescue device (p<0.001) decreased with increasing BMI category.

Devices placed in patients with obesity were less likely to be present on admission (p<0.001) and more likely to be present at discharge from the PICU (p=0.004), and remained in place for a longer total time in the PICU (median duration of device: obese 2.0 days, overweight 1.8 days, normal-weight 1.7 days, p<0.001), as shown in Table III. Broviacs and PICC lines were more likely to be present at discharge from the PICU than percutaneous CVCs (91% of broviacs and 86% of PICCs vs 29% of percutaneous CVCs, p<0.001, data not shown). After censoring these time calculations for devices being present on admission and discharge, the total device time did not differ significantly by BMI category, age, or gender.

Table III: Device time results by patient weight category

	Normal-Weight (N=47,792) Median (IQR)	Overweight (N=11,154) Median (IQR)	Obese (N=15,018) Median (IQR)	P value
Time of Placement after Admission (days)	1.5 (0.8-4.3)	1.5 (0.8-4.6)	1.6 (0.8-4.7)	0.019
Total Device Time (days)	8.3 (3.9-17.3)	8.5 (3.7-18.1)	8.3 (3.8-17.8)	0.31
Device Time in PICU (days)	1.7 (0.8-3.9)	1.8 (0.9-4.7)	2.0 (0.9-5.1)	<0.001

*Device time was missing for 674 records (440 normal-weight, 92 overweight, 142 obese)

100/142 (70%) of centers reported complications with vascular access devices, including 32,052 patients with devices placed. A total of 1427 complications were reported, with a slightly higher prevalence for patients with obesity (5.9% vs 4.0% in normal-weight patients, p<0.001). The prevalence of most types of complications differed by BMI category and are summarized in Table IV. Patients with obesity were more likely to experience mechanical issues and thrombosis.

Table IV: Device complications by patient weight category

	Normal-Weight (N=20,741) N (%)	Overweight (N=4872) N (%)	Obese (N=6439) N (%)	P value
Any Complication	827 (4.0%)	221 (4.5%)	379 (5.9%)	<0.001
Mechanical	257 (1.2%)	56 (1.2%)	127 (2.0%)	<0.001
Infection	111 (0.5%)	25 (0.5%)	41 (0.6%)	0.58
Thrombosis	103 (0.5%)	26 (0.5%)	49 (0.8%)	0.04
Bleeding	44 (0.2%)	13 (0.3%)	30 (0.5%)	0.003
Other	365 (1.8%)	115 (2.4%)	158 (2.5%)	<0.001

Following mixed-effects multivariable logistic regression, obesity was an independent negative predictor of device placement (see Table V). Obesity was positively associated with PICC placement (OR 1.21, 95% CI 1.14-1.27) and negatively associated with percutaneous CVC placement (OR 0.94, 95% CI 0.89-0.99). Post-operative status (HR 0.50, 95% CI 0.49-0.52), history of trauma (HR 1.58, 95% CI 1.52-1.63), and severity of illness (HR 1.29, 95% CI 1.19-1.40), but not weight status, were associated with total device time. Following mixed-effects multivariable logistic regression, obesity was an independent risk factor for developing a complication, with an odds ratio of 1.30 (95% CI 1.14-1.48).

Table V: Multivariable logistic regression analyses

	Odds Ratio (95% CI)
Placement of any vascular access device	
Obese vs normal-weight	0.96 (0.92-0.99)
Overweight vs normal-weight	0.96 (0.92-1.00)
6-12 years vs 2-5 years	1.42 (1.37-1.47)
13-18 years vs 2-5 years	1.61 (1.56-1.67)
PIM2 ROM <0.05 vs 0	3.08 (2.98-3.19)
PIM2 ROM 0.05-0.1 vs 0	9.71 (8.97-10.5)
PIM2 ROM >0.1 vs 0	28.2 (25.8-30.9)
Female sex	1.18 (1.14-1.21)
Post-operative	9.79 (9.49-10.1)
Trauma	0.57 (0.54-0.59)
Placement of a rescue device (percutaneous CVC, PICC, broviac)	
Obese vs normal-weight	0.97 (0.93-1.02)
Overweight vs normal-weight	1.03 (0.99-1.08)
6-12 years vs 2-5 years	1.07 (1.03-1.12)
13-18 years vs 2-5 years	1.04 (1.00-1.08)
PIM2 ROM <0.05 vs 0	4.42 (4.27-4.58)
PIM2 ROM 0.05-0.1 vs 0	10.7 (9.96-11.5)
PIM2 ROM >0.1 vs 0	31.5 (29.0-34.1)
Female sex	1.07 (1.04-1.11)
Post-operative	3.05 (2.94-3.15)
Trauma	0.72 (0.68-0.76)
Placement of a PICC line	
Obese vs normal-weight	1.21 (1.14-1.27)
Overweight vs normal-weight	1.06 (0.99-1.13)
6-12 years vs 2-5 years	1.27 (1.20-1.34)
13-18 years vs 2-5 years	1.23 (1.16-1.30)
PIM2 ROM <0.05 vs 0	2.64 (2.52-2.78)
PIM2 ROM 0.05-0.1 vs 0	5.40 (4.94-5.91)
PIM2 ROM >0.1 vs 0	4.79 (4.37-5.26)
Female sex	1.08 (1.03-1.13)
Post-operative	1.10 (1.05-1.16)
Trauma	0.68 (0.63-0.73)
Placement of a percutaneous CVC	
Obese vs normal-weight	0.94 (0.89-0.99)
Overweight vs normal-weight	0.97 (0.93-1.02)
6-12 years vs 2-5 years	1.00 (0.95-1.05)
13-18 years vs 2-5 years	1.00 (0.95-1.04)
PIM2 ROM <0.05 vs 0	5.11 (4.90-5.34)
PIM2 ROM 0.05-0.1 vs 0	10.1 (9.34-11.0)
PIM2 ROM >0.1 vs 0	44.5 (41.0-48.2)
Female sex	1.09 (1.05-1.13)
Post-operative	4.28 (4.11-4.46)
Trauma	1.00 (0.95-1.07)
Placement of a broviac	
Obese vs normal-weight	1.01 (0.90-1.14)
Overweight vs normal-weight	1.08 (0.94-1.14)
6-12 years vs 2-5 years	0.80 (0.72-0.90)
13-18 years vs 2-5 years	0.64 (0.57-0.72)
PIM2 ROM <0.05 vs 0	2.85 (2.56-3.17)
PIM2 ROM 0.05-0.1 vs 0	7.87 (6.71-9.24)
PIM2 ROM >0.1 vs 0	5.34 (4.42-6.46)
Female sex	0.94 (0.86-1.03)

Post-operative	1.38 (1.25-1.53)
Trauma	0.12 (0.09-0.17)
Occurrence of any complication	
Obese vs normal-weight	1.30 (1.14-1.48)
Overweight vs normal-weight	1.04 (0.89-1.22)
6-12 years vs 2-5 years	0.78 (0.78-0.89)
13-18 years vs 2-5 years	0.82 (0.71-0.94)
PIM2 ROM <0.05 vs 0	1.87 (1.86-2.82)
PIM2 ROM 0.05-0.1 vs 0	2.29 (1.86-2.82)
PIM2 ROM >0.1 vs 0	3.20 (2.66-3.85)
Female sex	1.07 (0.95-1.19)
Post-operative	0.53 (0.47-0.61)
Trauma	1.32 (1.12-1.56)
Total device time hazard ratios (censored)	
Obese vs normal-weight	0.99 (0.95-1.02)
Overweight vs normal-weight	0.96 (0.92-1.00)
PIM-2 score	1.29 (1.19-1.40)
Female sex	0.98 (0.95-1.01)
Post-operative	0.50 (0.49-0.52)
Trauma	1.58 (1.52-1.63)

Discussion:

To our knowledge, this is the first study to assess the requirement for vascular access in a critically ill pediatric population by weight status. We found that patients with obesity were less likely to undergo placement of a CVC but that, once placed, those CVCs were more likely to be present at discharge from the PICU. This may reflect clinician concerns about obtaining and maintaining access in these patients or could represent different diagnoses or stages of illness at the time of discharge. We had hypothesized that more CVCs would be needed for these patients due to anatomic difficulties establishing access prohibiting the use of PIVs. The placement of fewer CVCs in children with obesity could still reflect anatomic difficulties, as device placement attempts which were ultimately unsuccessful may not be captured.

Timely establishment of vascular access is necessary for good clinical outcomes. Children with obesity were less likely to have a CVC placed prior to PICU admission, and placement was slightly delayed in patients with obesity compared to normal-weight or overweight following PICU admission. Although the total device time is estimated to be equal, children with obesity have a longer device time in the PICU and are more likely to leave the PICU with a vascular access device. The incidence of complications increases with prolonged use of a CVC,[75] so prompt removal is important in preventing adverse patient safety events.

Patients with obesity were more likely to experience complications related to their CVC. Of note, the 4.5% prevalence of complications in this cohort is lower than that previously reported in the literature.[19] Thrombosis was more common in patients with obesity, as has previously been reported for hospitalized pediatric patients.[67,68] Although some prior studies suggest that patients with obesity may be at higher risk for infection,[7,76] we did not see a clear difference in prevalence of infectious complications compared to normal-weight patients. The low numbers of reported complications, even in this large database, limits this analysis. The overall incidence of complications was higher for children with obesity and only included complications reported from the PICU. Since more children with obesity were discharged from the PICU with their device (mainly PICC lines and Broviac catheters) in place, we anticipate that there may be an even greater disparity in complication rate than we reported here. Future studies could investigate obesity as a risk factor for CVC complications in more detail.

A strength of this study is the use of the large, nationally representative VPS database. Notably, the prevalence of obesity in this cohort (21%) is higher than the national average of 17%. This may be related to the older age of our cohort compared to US census data[77] and the higher prevalence of obesity at older ages.[1,78] The relative rates of hospitalization and requirement for critical care between patients of different weight classes are unknown.

There are several limitations to this study. For this analysis, we only included patients with a measured and physiologically plausible height and weight. This excluded nearly 50% of admissions in the database, most of which were missing heights. Some types of units may be more likely than others to report height, which could bias our results. The need for CVC placement can be influenced by the relative success of peripheral IV placement. Especially in patients with obesity, success may depend on provider skill and use of ultrasound,[79] none of which are captured in this dataset. As previously stated, CVC complications was not a required element in this database, which may bias our results based on the characteristics of centers that did report these findings. We have limited information on the medical decision-making around CVC placement and removal in this study. The database only includes subject information during PICU admission, so data on vascular device removal, further complications, and effects on the remainder of the hospital stay are not available. Detailed retrospective chart review at individual sites or a prospective study may be helpful in identifying potential interventions to decrease vascular access complications for patients with obesity.

Overall, our study of a large database of United States PICUs found that obesity was associated with decreased likelihood of placement of a vascular access device but increased likelihood of device-related complications. Future prospective studies could better assess the incidence and, ultimately, prevention of complications associated with these devices to improve clinical outcomes in critically-ill children with obesity.

CHAPTER THREE

Background:

The primary exposure in this study is patient's BMI category, traditionally classified into normal-weight, overweight, and obese. Some literature suggests that obesity should be further subdivided, as there may be physiologic differences for both adults and children with the most severe forms of obesity.[80,81] Therefore, additional classifications of Class 1 obesity (100-120% of 95% BMI), Class 2 obesity (120-140% of 95% BMI or BMI>35), and Class 3 obesity (>140% of 95% BMI or BMI >40) have been proposed.[82,83] More severe forms of obesity have previously been associated with increased cardiometabolic risk among children and adolescents,[80,84] and the prevalence of severe obesity continues to increase in the United States.[2,85]

Classification of Severe Obesity:

We therefore repeated our primary analyses with our subjects classified as described above into normal-weight (N=75,995, 63%), overweight (N=18,854, 16%), class 1 obesity (N=16,514, 13%), class 2 obesity (N=5526, 5%), and class 3 obesity (N=3587, 3%). This prevalence is similar to the nationally reported prevalence of 6.3% for class 2 obesity and 2.4% for class 3 obesity, based on National Health and Nutrition Examination Survey data from 2013-2014.[85] When reviewing the demographics, we found expected differences in the prevalence of severe obesity by age, sex, and race/ethnicity, as seen in Table VI, with higher prevalence among older children, males, Hispanic children, and black children. The trends we saw previously toward fewer scheduled admissions related to operations seemed to be true predominantly for class 1 and 2 obesity, but not for class 3. Patients with obesity are often considered inferior surgical candidates due to anesthesia risk and difficulty completing the surgery itself. It would be interesting to identify the types and urgency of the procedures performed on subjects of different weight classes. Admissions secondary to trauma seemed to decrease with increasing obesity severity (11% vs 9% vs 6%, $p<0.001$).

Table VI: Patient and device placement characteristics by weight category (severe obesity)

	Normal-Weight (N=75,995) N (%)	Overweight (N=18,854) N (%)	Class 1 (N=16,514) N (%)	Class 2 (N=5526) N (%)	Class 3 (N=3383) N (%)	P value
Age						
2-5 years	25,254 (33%)	5278 (28%)	5969 (36%)	1172 (21%)	518 (15%)	
6-12 years	25,497 (34%)	6765 (36%)	5596 (34%)	2248 (41%)	1436 (43%)	<0.001
13-18 years	25,244 (33%)	6811 (36%)	4949 (30%)	2106 (38%)	1429 (42%)	
Male	40,626 (54%)	9886 (52%)	9560 (58%)	3158 (57%)	1930 (57%)	<0.001
Race/Ethnicity						
White	38,877 (55%)	9215 (52%)	7567 (49%)	2366 (46%)	1321 (42%)	
Black	13,718 (19%)	3641 (21%)	3332 (22%)	1253 (24%)	992 (31%)	<0.001
Hispanic	10,317 (15%)	2914 (17%)	2868 (19%)	1028 (20%)	559 (18%)	
Other	7841 (11%)	1854 (11%)	1721 (11%)	526 (10%)	296 (9%)	
PIM-2 Mortality Risk Mean % (SD)	1.77 (7.49)	1.96 (8.46)	2.03 (8.43)	1.77 (7.58)	1.59 (7.26)	<0.001
Unscheduled Admission	53,171 (70%)	13,975 (74%)	12,457 (75%)	4201 (76%)	2461 (73%)	<0.001
Post-operative	28,230 (37%)	6319 (34%)	5400 (33%)	1835 (33%)	1245 (37%)	<0.001
Trauma	8445 (11%)	2277 (12%)	1811 (11%)	511 (9%)	208 (6%)	<0.001
PICU LOS (days) Median (IQR)	1.26 (0.86-2.59)	1.30 (0.85-2.70)	1.40 (0.87-2.82)	1.43 (0.87-2.88)	1.39 (0.86-2.86)	<0.001
Vascular Access						
Any Device	29,491 (39%)	6856 (36%)	6045 (37%)	1952 (35%)	1065 (32%)	<0.001
Rescue CVC	17,419 (23%)	3982 (21%)	3632 (22%)	1157 (21%)	633 (19%)	<0.001
Device Type						
Arterial	22,888 (30%)	5139 (27%)	4423 (27%)	1390 (25%)	749 (22%)	<0.001
Percutaneous CVC	12,458 (16%)	2705 (14%)	2450 (15%)	731 (13%)	379 (11%)	<0.001
PICC	5330 (7%)	1399 (7%)	1336 (8%)	482 (9%)	280 (8%)	<0.001
Port-a-cath	1840 (2%)	454 (2%)	434 (3%)	133 (2%)	54 (2%)	0.013
Hemodialysis	1266 (2%)	384 (2%)	338 (2%)	112 (2%)	84 (2%)	<0.001
Broviac	1163 (2%)	304 (2%)	262 (2%)	82 (1%)	51 (2%)	0.91
Device Present						
Admission	21,335 (28%)	4680 (25%)	3947 (24%)	1265 (23%)	609 (18%)	<0.001
Discharge	11,212 (15%)	2808 (15%)	2597 (16%)	882 (16%)	492 (15%)	0.005

*Race/ethnicity data was missing for 8066 subjects (5242 normal-weight, 1230 overweight, 1026 Class 1 obesity, 353 Class 2 obesity, 215 Class 3 obesity)

Severe obesity had a significant negative association with our primary outcome, placement of any vascular access device. In the bivariate analysis, the percentage of patients with any device placed decreased with increasing class of obesity (37% vs 35% vs 32%, $p<0.001$). These results were similar when looking at placement of a venous rescue device (22% vs 21% vs 19%, $p<0.001$). The trends in type of device placed were also amplified for severe obesity compared to our previous results; increasing obesity was associated with decreasing likelihood of percutaneous CVC placement and increasing likelihood of PICC placement, as shown in Table VI. Those devices were much less likely to be present on admission for subjects with severe obesity and were present for a prolonged time in the PICU, although the total device time remained similar across weight categories (Table VII).

Table VII: Device time results by patient weight category (severe obesity)

	Normal-Weight (N=75,995) N (%) or Median (IQR)	Overweight (N=18,854) N (%) or Median (IQR)	Class 1 (N=16,514) N (%) or Median (IQR)	Class 2 (N=5526) N (%) or Median (IQR)	Class 3 (N=3383) N (%) or Median (IQR)	P value
Time of Placement after Admission (days)	1.5 (0.8-4.3)	1.5 (0.8-4.6)	1.6 (0.8-4.6)	1.6 (0.8-4.6)	1.7 (0.9-5.4)	<0.001
Total Device Time (days)	8.3 (3.9-17.3)	8.5 (3.7-18.1)	8.4 (3.8-17.1)	7.9 (3.8-18.5)	8.1 (3.6-18.6)	0.22
Device Time in PICU (days)	1.7 (0.8-3.9)	1.8 (0.9-4.7)	1.9 (0.9-5.0)	2.0 (0.9-5.2)	2.2 (0.9-6.0)	<0.001

Table VIII: Device complications by patient weight category (severe obesity)

	Normal-Weight (N=20,741) N (%)	Overweight (N=4872) N (%)	Class 1 (N=4241) N (%)	Class 2 (N=1405) N (%)	Class 3 (N=793) N (%)	P value
Any Complication	827 (4.0%)	221 (4.5%)	257 (6.1%)	71 (5.1%)	51 (6.4%)	<0.001
Mechanical	257 (1.2%)	56 (1.2%)	78 (1.8%)	26 (1.9%)	23 (2.9%)	<0.001
Infection	111 (0.5%)	25 (0.5%)	28 (0.7%)	8 (0.6%)	5 (0.6%)	0.87
Thrombosis	103 (0.5%)	26 (0.5%)	37 (0.9%)	8 (0.6%)	4 (0.5%)	0.06
Bleeding	44 (0.2%)	13 (0.3%)	20 (0.5%)	5 (0.4%)	5 (0.6%)	0.011
Other	365 (1.8%)	115 (2.4%)	106 (2.5%)	30 (2.1%)	22 (2.8%)	0.002

The strength of the associations with severe obesity were demonstrated in the multivariable analysis. We found that obesity overall was associated with an odds ratio of 0.96 (0.92-0.99) for placement of any vascular access device. When additional categories were applied, we had no significant finding for class 1 obesity and a similar odds ratio to our previous analysis for class 2 obesity (OR 0.93, 95% CI 0.86-0.99), as shown in Table IX. However, class 3 obesity was associated with an odds ratio of 0.69 (0.63-0.75) for placement of any vascular access device when compared to normal-weight. Results were similar for placement of a percutaneous CVC. This suggests that anatomic considerations affecting vascular access may become an issue only when obesity is severe.

Table IX: Multivariable logistic regression (severe obesity)

	Odds Ratio (95% CI)
Placement of any vascular access device	
Class 3 vs normal-weight	0.69 (0.63-0.75)
Class 2 vs normal-weight	0.93 (0.86-0.99)
Class 1 vs normal-weight	1.04 (0.99-1.08)
Overweight vs normal-weight	0.96 (0.92-1.00)
Placement of a rescue device (percutaneous CVC, PICC, broviac)	
Class 3 vs normal-weight	0.95 (0.86-1.04)
Class 2 vs normal-weight	1.05 (0.97-1.13)
Class 1 vs normal-weight	1.05 (1.01-1.10)
Overweight vs normal-weight	1.03 (0.99-1.08)
Placement of a PICC line	
Class 3 vs normal-weight	1.26 (1.11-1.43)
Class 2 vs normal-weight	1.29 (1.17-1.43)
Class 1 vs normal-weight	1.17 (1.10-1.24)
Overweight vs normal-weight	1.06 (0.99-1.13)
Placement of a percutaneous CVC	
Class 3 vs normal-weight	0.83 (0.73-0.94)
Class 2 vs normal-weight	0.94 (0.85-1.03)
Class 1 vs normal-weight	1.01 (0.96-1.07)
Overweight vs normal-weight	0.97 (0.93-1.02)
Placement of a broviac	
Class 3 vs normal-weight	1.04 (0.78-1.39)
Class 2 vs normal-weight	1.01 (0.80-1.27)
Class 1 vs normal-weight	1.01 (0.88-1.16)
Overweight vs normal-weight	1.08 (0.94-1.22)
Occurrence of any complication	
Class 3 vs normal-weight	1.51 (1.12-2.05)
Class 2 vs normal-weight	1.12 (0.86-1.45)
Class 1 vs normal-weight	1.32 (1.14-1.54)
Overweight vs normal-weight	1.04 (0.89-1.22)
Total device time hazard ratios (censored)	
Class 3 vs normal-weight	0.97 (0.90-1.05)
Class 2 vs normal-weight	0.96 (0.90-1.02)
Class 1 vs normal-weight	1.00 (0.96-1.04)
Overweight vs normal-weight	0.96 (0.92-1.00)

Severe obesity is also strongly associated with the incidence of CVC complications. Subjects with class 3 obesity had an odds ratio of 1.51 (1.12-2.05) for the occurrence of any complication compared to those of normal weight. Interestingly, those with class 1 obesity were also more likely to experience a complication (OR 1.32, 95% CI 1.14-1.54), but those with class 2 obesity were not. Complication data are shown in Table VIII; this analysis was likely limited by small sample sizes in the setting of a larger number of categories.

Overall, these findings suggest that the most severe forms of obesity drive the association we identified previously between obesity and difficulties with vascular access. Children with severe obesity are less likely to have access obtained and more likely to experience complications with devices that are placed. Hospitals wishing to improve the quality of care for children with obesity may need to focus their efforts on the children most severely affected.

Multiple Imputation Analysis:

Whether analyzing obesity with single or multiple categories, accurate analysis depends on correct calculation of BMI. To calculate BMI in pediatrics, the patient's age, sex, height, and weight are all necessary. Age, sex, and weight are routinely collected during the provision of clinical care, but height is often not assessed, especially in critically ill patients.[86] Age, sex, and weight alone can be used to determine the subject's weight-for-age z-score per Centers for Disease Control and Prevention guidelines.[72,74] Although this has not been extensively studied as an alternative exposure to assess the effects of obesity, Ross et al found it was inferior to BMI z-score in assessing risk of mortality among pediatric patients in the VPS database.[6]

Nearly half of the admissions (175,373 out of 365,371) included in the VPS database for the timeframe of this study were missing information on height. Hospital characteristics vary between centers that report height and those that do not. Academic centers, which represent 70% of all hospitals submitting data to VPS, were more likely to report height (43% vs 36%, p<0.001). Centers with 24/7 attending coverage (37% overall) were less likely to report height (36% vs 64%, p<0.001). Finally, medium -sized units (20-29 beds) were more likely to report height than smaller or larger units (p<0.001). Since height data may not be missing completely at random, it is possible that our complete case analysis described in chapter 2 introduced bias into our parameter estimates. It is likely that the height data is missing at random, because it is unlikely that the value of height itself affects missingness, but other collected variables (described above) do affect missingness.

In order to address this concern, we assessed the correlation between BMI z-score and weight-for-age z-score among those subjects with age, sex, height, and weight documented. We found a moderate correlation, with a Pearson correlation coefficient of 0.82, a Spearman correlation coefficient of 0.72, and a Kendall correlation coefficient of 0.55. Therefore we might expect similar trends if we examined vascular access using weight-for-age (which was available for all subjects) as an exposure rather than BMI. Ross et al used both exposures, BMI-for-age and weight-for-age, when investigating mortality using the VPS database. [6] They found that the trends were similar, but that the overall curve was shifted to the right when using weight-for-age, falsely suggesting a protective effect of mild obesity. Given this prior experience with VPS data, we explored other options to incorporate all subjects into the analysis.

For our strategy, we first set height and weight outliers to missing. We then performed multiple imputation to ensure height and weight were available for all subjects. Since few weights were missing and no sex or age values were missing, we first used Markov Chain Monte Carlo to impute enough weight values to make the missingness pattern monotone, followed by regression imputation for the missing heights. We then repeated our mixed-effects logistic regression analyses using the imputed dataset, with results summarized in Table X. Although there are small differences in the odds ratios obtained, none represent a clinically significant change from the results obtained with recorded heights and weights, including the analysis with severe obesity. This is reassuring that our original findings were not biased by differential loss of data based on which centers routinely reported heights.

Table X: Multivariable logistic regression (multiple imputation)

	Odds Ratio (95% CI)
Placement of any vascular access device	
Class 3 vs normal-weight	0.76 (0.71-0.82)
Class 2 vs normal-weight	0.94 (0.90-0.99)
Class 1 vs normal-weight	0.99 (0.95-1.02)
Overweight vs normal-weight	0.99 (0.95-1.02)
Female sex	1.14 (1.12-1.16)
Post-operative	6.37 (6.24-6.43)
Trauma	0.81 (0.78-0.84)
Placement of a rescue device (CVC, PICC, Broviac)	
Class 3 vs normal-weight	0.96 (0.89-1.03)
Class 2 vs normal-weight	1.03 (0.97-1.08)
Class 1 vs normal-weight	1.03 (0.99-1.07)
Overweight vs normal-weight	0.98 (0.99-1.07)
Female sex	1.02 (1.00-1.04)
Post-operative	2.06 (2.01-2.11)
Trauma	1.04 (1.00-1.07)
Placement of a PICC line	
Class 3 vs normal-weight	1.24 (1.12-1.36)
Class 2 vs normal-weight	1.21 (1.12-1.31)
Class 1 vs normal-weight	1.11 (1.05-1.17)
Overweight vs normal-weight	1.04 (0.99-1.11)
Female sex	1.05 (1.01-1.08)
Post-operative	0.97 (0.93-1.00)
Trauma	0.85 (0.80-0.90)
Placement of a percutaneous CVC	
Class 3 vs normal-weight	0.86 (0.78-0.95)
Class 2 vs normal-weight	0.96 (0.89-1.03)
Class 1 vs normal-weight	1.01 (0.96-1.05)
Overweight vs normal-weight	0.95 (0.91-0.99)
Female sex	1.02 (1.00-1.05)
Post-operative	2.65 (2.58-2.73)
Trauma	1.43 (1.37-1.48)
Placement of a Broviac	
Class 3 vs normal-weight	0.89 (0.71-1.12)
Class 2 vs normal-weight	0.94 (0.78-1.13)
Class 1 vs normal-weight	1.01 (0.89-1.15)
Overweight vs normal-weight	1.01 (0.89-1.13)
Female sex	0.94 (0.87-1.02)
Post-operative	1.13 (1.04-1.22)
Trauma	0.14 (0.10-0.18)

Future Studies:

These findings directly inform several future lines of investigation. The association of obesity, especially severe obesity, with vascular access complications is interesting but limited by incomplete reporting. Future studies could continue to use the

VPS database but could identify complications by diagnosis code rather than center report. This study could also collect information on CVC location, which has been shown to influence complication rates in adults with obesity.[50] As an alternative, a prospective study could also address this question well but would need to be multi-center in order to be adequately powered for this relatively rare outcome. A clinical trial could assess potential interventions such as use of ultrasound to improve success of vascular access placement for children with severe obesity. Finally, quality improvement initiatives could be used to implement proven strategies for the prevention of complications such as thrombosis.

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support team improves nutritional status assessment of the critically ill child. Pediatr Crit Care Med 16[3], e82-e88. 2015.

WAKE FOREST SCHOOL OF MEDICINE

Curriculum Vitae

NAME:	Elizabeth Eby Halvorson, MD, FAAP
CURRENT ACADEMIC TITLE:	Assistant Professor
ADDRESS:	Department of Pediatrics Wake Forest School of Medicine Medical Center Boulevard Winston-Salem, NC 27157-1010 (336) 716-4999 (office) (336) 806-6638 (pager) (336) 713-9387 (fax) E-mail: ehalvors@wakehealth.edu

EDUCATION:

2000-2004	University of California, Berkeley Berkeley, CA B.S. Chemistry with Honors
2004-2009	Vanderbilt University School of Medicine Nashville, TN M.D.
2014-Present	Wake Forest University Winston-Salem, NC M.S. Clinical and Population Translational Science

POSTDOCTORAL TRAINING:

2009-2012	Resident, Pediatrics Wake Forest Baptist Medical Center Winston-Salem, NC
2012-2013	Chief Resident, Pediatrics Wake Forest Baptist Medical Center Winston-Salem, NC

PROFESSIONAL LICENSURE:

2012-present	State of North Carolina, #2012-00431

SPECIALTY CERTIFICATION:

2012	Diplomate, American Board of Pediatrics

EMPLOYMENT:

Academic Appointments (in chronologic order):

2012-2013	Chief Resident, Department of Pediatrics Wake Forest School of Medicine
2012-2014	Instructor, Department of Pediatrics Wake Forest School of Medicine
2014-Present	Assistant Professor, Dept of Pediatrics Wake Forest School of Medicine

Professional Experience

2012-Present	Pediatric Hospitalist Wilkes Regional Medical Center Wilkesboro, NC

OTHER PROFESSIONAL APPOINTMENTS AND INSTITUTIONAL SERVICE:

Institutional Committee Service (in chronologic order):

2012-2013	Pharmacy & Therapeutics
2015-2016	Graduate School Honor Code Panel

Departmental Committee Service (in chronologic order):

2011-2012	Admissions Process Committee
2011-2015, 2016-Present	Faculty/Housestaff Committee
2011-2013	Pediatric Center of Excellence Committee
2012-2013	Grand Rounds Planning Committee
2012-2013	Brenner Children's Hospital Morbidity and Mortality Committee
2012-2015	Brenner Children's Hospital Inpatient Committee [Leader]
2012-Present	Hospitalist Clinical Guideline Working Group: Rule-out Sepsis
2013-Present	Brenner Children's Hospital Quality and Safety Committee
2013-2014	Family-Centered Rounds QI Group
2013-Present	Pediatric Key Educational Faculty
2014-Present	Pediatric Residency Program Evaluation Committee
2015-Present	Hospitalist Clinical Guideline Working Group: ALTE
2015-Present	Brenner Children's Hospital Acute Care Quality Committee

Administrative Roles (in chronologic order):

2013-Present	PA Student Pediatrics Rotation Director
2013-Present	Pediatric Residency Global Health Pathway Mentor
2013-2015	8th floor Ardmore West Medical Director
2013-2014	Implementation Owner, CAP FY13-33
2016 – Present	Year III Clinical Coach, Pediatrics Clerkship

EXTRAMURAL APPOINTMENTS AND SERVICE:

Journal Reviewer:	Clinical Pediatrics, Hospital Pediatrics, Scientific Reports, Journal of Neuroscience in Rural Practice
Conference Reviewer:	Pediatric Academic Society 2015/2016, Pediatric Hospital Medicine 2015
Moderator:	Pediatric Academic Society 2016

PROFESSIONAL MEMBERSHIPS:

2009-Present	American Academy of Pediatrics
2013-Present	Academic Pediatric Association
2016-Present	The Obesity Society

HONORS AND AWARDS:

2014	Outstanding Pediatrics: Best Teachers 2013-14
2014-2016	Academic Pediatric Association Research Scholar
2013	"You Make the Difference" Award
2013	Wake Forest Translational Science Research Scholar
2011, 2013	Wake Forest SOM Pennell Pro Humanitate Vitae Award
2009	Alpha Omega Alpha
2004-2009	Vanderbilt University SOM Canby Robinson Scholarship
2002	Undergraduate Research Apprentice Program Award
2000-2004	UC Berkeley Regents' Scholarship
2000	National Merit Scholar

PUBLIC OUTREACH:

2013-Present	International Collaborative with Tamale Teaching Hospital Tamale, Ghana

BIBLIOGRAPHY:

Peer-Reviewed Journal Articles:

1) Buehring GC, **Eby E**, Eby MJ. (2004) Cell line cross-contamination: how aware are mammalian cell culturists of the problem and how to monitor it? In Vitro Cell Dev Biol Anim. 40(7), 211-5. PMID 15638703

2) Kobayashi T, Antar AAR, Boehme KW, Danthi P, **Eby E**, Guglielmi KM, Holm GH, Johnson EM, Maginnis MS, Naik S, Skelton WB, Wetzel JD, Wilson GJ, Chappell JD, Dermody TS. (2007) A plasmid-based reverse genetics system for animal double-stranded RNA viruses. Cell Host & Microbe. 1(2), 147-57. PMID 18005692

3) Sagerman PJ, McBride AS, **Halvorson EE**. (2010) Wound Care. Pediatric Emergency Medicine Practice. 7(9): 1-23.

4) Reiter DM, Frierson JM, **Halvorson EE**, Kobayashi T, Dermody TS, Stehle T. (2011) Crystal structure of reovirus attachment protein σ1 in complex with sialylated oligosaccharides. PLoS Pathogens. 7(8). PMID 21829363

5) **Halvorson EE**, Skelton J. (2012) Appointment attendance in a pediatric weight management program. Clinical Pediatrics, 51(9), 888-91. PMID 21622690

6) **Halvorson EE**, Poehling K, Peters T. (2012) Potential impact of accelerating the primary dose of rotavirus vaccine in infants. Vaccine. 30(17), 2738-41. PMID 22374373

7) **Halvorson EE**, Chandler N, Neiberg R, Ervin S. (2013) Association of NPO Status and type of nutritional support on weight and length of stay in infants hospitalized with bronchiolitis. Hospital Pediatrics. 3(4),366-70. PMID 24435195

8) **Halvorson EE**, Irby M, Skelton JA. (2014) Pediatric obesity and safety in inpatient settings: a systematic literature review. Clinical Pediatrics. 53(10), 975-987. PMID 24803638

9) **Halvorson EE**, Hayes N. (2015) Tachypnea since birth with worsening cough in a term female. Wake Forest Journal of Science and Medicine. 1(1), 37-38.

10) Brown CL, **Halvorson EE**, Cohen G, Lazoricks S, Skelton JA. (2015) Addressing Childhood Obesity: Opportunities for Prevention. Pediatric Clinics of North America. 62(5):1241-1261. PMID 26318950

11) **Halvorson EE**, Ervin SE, Russell TB, Skelton JA, Davis S, Spangler J. (2016) Association of obesity and pediatric venous thromboembolism. Hospital Pediatrics. 6(1):22-26. PMID 26675300

<u>Books:</u>

1) **Eby E** [Editor] in Le T, Krause K, Senior Editors. First Aid Basic Sciences - General Principles/Organ Systems. New York: McGraw-Hill, 1st edition. 2008.

2) Le T, **Halvorson EE** [Senior Editor]. First Aid Cases for the USMLE Step 2 CK. New York: McGraw-Hill, 2nd edition. 2009.

3) **Halvorson EE** [Editor] in Le T, Krause K, Senior Editors. First Aid Basic Sciences - Organ Systems. New York: McGraw-Hill, 2nd edition. 2012.

4) **Halvorson EE**. "Abdominal Masses" in Rauch DA, Gershel JC. Caring for the Hospitalized Child: a handbook of inpatient pediatrics, 2^{nd} edition. 2016.

Miscellaneous:

1) **Halvorson EE**, Goodpasture M. "Child Abuse or Mimic: Two Cases of Perianal Redness - Case One" Consultant for Pediatricians. 2012 April. 11(4):113-114.

Abstracts/Scientific exhibits/Presentations at national meetings:

1) Balaguer JM, **Eby E**, Cai S, et al. "Stroke reduction in coronary surgery using a simple intraoperative strategy in a high-risk patient population" [Oral Abstract Presentation by Balaguer JM]19th Congress of the World Society of Cardiothoracic Surgeons, 2009 Nov 5. Buenos Aires, Argentina.

2) **Halvorson EE**, Poehling K, Peters T. "Potential impact of accelerating the primary dose of rotavirus vaccine in infants." [Poster Presentation by Halvorson EE] 2010 Pediatric Academic Society Annual Meeting, 2010 May 2. Vancouver, Canada.

3) **Halvorson EE**, Goodpasture M. "Diagnosis of Perineal Groove in a Newborn Female" [Poster Presentation by Halvorson EE] 2010 North Carolina Pediatric Society Annual Meeting, 2010 July 30. Myrtle Beach, SC.

4) **Halvorson EE**, Skelton J. "Appointment Attendance in a Pediatric Weight Management Program" [Poster Presentation by Halvorson EE] Obesity 2010: The 28th Annual Scientific Meeting of the Obesity Society, 2010 Oct 10. San Diego, CA.

5) Rajabi F, **Halvorson EE**, Ajizian S, McLean T, Ervin S. "Cystic Lung Lesions: Two Cases Illustrating a Broad Differential" [Poster Presentation by Rajabi F] 2011 North Carolina Pediatric Society Annual Meeting, 2011 Aug 20. Asheville, NC. [Honorable Mention]

6) **Halvorson EE**, Chandler N, Ervin SE. "Effect of NPO Status on Weight in Bronchiolitis Patients." [Poster Presentation by Halvorson EE] 2012 Pediatric Hospital Medicine Annual Meeting, 2012 July 20. Covington, KY.

7) **Halvorson EE**, Irby M, Skelton JA. "Pediatric Obesity and Patient Safety: A Systematic Review." [Poster Presentation by Halvorson EE] 2013 Pediatric Hospital Medicine Annual Meeting, 2013 Aug 2. New Orleans, LA.

8) Sharpe B, Goslings S, **Halvorson EE**, Pomeroy B. "Building Effective Mini-Lectures for Teaching on the Wards." [Workshop] 2014 Pediatric Hospital Medicine Annual Meeting. 2014 July 26. Orlando, FL.

9) **Halvorson EE**, Ervin S, Russell T, Skelton JA, Davis S, Spangler J. "Obesity as a Risk Factor for Pediatric Venous Thromboembolism." [Poster Presentation by Halvorson

EE] Obesity Week 2014: The Obesity Society's Annual Meeting, 2014 November 6. Boston, MA.

10) **Halvorson EE**, Peters T, Skelton JA, Suerken C, Snively B, Poehling K. "Is Weight Associated with Severity of Acute Respiratory Illness in Children?" [Poster Presentation by Halvorson EE] 2015 Pediatric Academic Society Annual Meeting. 2015 April 28. San Diego, CA.

11) **Halvorson EE**, Skelton JA, Case D, McCrory M. "Vascular access in critically ill pediatric patients with obesity." [Poster Presentation by Halvorson EE]. 2016 Pediatric Academic Society Annual Meeting. 2016 May 2. Baltimore, MD.

12) Potisek N, **Halvorson EE**, Wood JK, Skelton JA. "Characteristics of Children Hospitalized for Management of Constipation." [Poster Presentation by Potisek N]. 2016 Pediatric Academic Society Annual Meeting. 2016 April 30. Baltimore, MD.

ADVISING

Resident and Fellows:

2013-present	Pediatrics Residency Global Health Pathway *Supervised 1 resident to date*
2016 – Present	Class Advisor, Pediatric Residency Class of 2019

Medical Students:

Fall 2015	Ashmitha Raja, MBBS Clinical Observership
Summer 2015	Thomas Curley (Rising 2nd year student) NIH Medical Student Research Program (MSRP) Project: Anti-Obesity Stigma in Pediatric Acute Care T2 Bedside to Community Translational Research Award
Summer 2016	Mariah Wright (Rising 2nd year student) NIH Medical Student Research Program (MSRP) Project: Anti-Obesity Stigma in Pediatric Acute Care
Summer 2016	Anuj Bhatia (St. George's University SOM, Grenada) Research Assistant
2016-2017	Sara Beverly (4th year student) Project: Patient Safety Events on the Pediatric Wards

Undergraduate Students:

2014 – Present	Salem College Undergraduate Student Internship *Supervised 1-2 students per year for 1 month internship*