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Hospital Emergency Room Visits for Heavy Menstrual Bleeding

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This is to certify that the doctoral dissertation by

Henry Mead

has been found to be complete and satisfactory in all respects,
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the review committee have been made.

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Walden University
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Abstract

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by

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MBA, City University, 1989

MPA, City University, 1996

BSc, University of British Columbia, 1978

Dissertation Submitted in Partial Fulfillment

of the Requirements for the Degree of

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Abstract

Heavy menstrual bleeding (HMB) is a well-recognized health issue among women of reproductive age. The characteristics and demographics of women in the community with HMB who present at the emergency department (ED) are not well described. This research aimed to describe the cohort of women who seek treatment at the ED. The Healthcare Cost and Utilization Project 2016 National Emergency Department Sample was examined. The theory of reasoned action predicts that women who present at the ED are exhibiting health seeking behavior. From 32 million records, the inception cohort identified N = 111,555 cases. Using national estimation weights, this translates to approximately 509,833 ED visits in the United States for HMB. The majority of the cohort, 39.59%, came from the lowest median household income quartile by ZIP code (under $42,999). Women with anemia were significantly older than the overall cohort. The greatest incidence of anemia was in women aged 40 to 49 years, 7.41%. Four logistic regression models examining the whole cohort and three comorbidities (anemia, hypertension, and diabetes) found age to be a significant predictor of hospitalization. Low income was also a significant predictor of hospitalization. The proportion hospitalized in the lowest household income group was significantly greater versus each of the other three quartiles, $p < 0.001$. Women living in the rural locations with the lowest household income had the highest proportion of hospitalizations. Women of economic disadvantage are most likely to use the ED for medical care. Residing in rural areas may lead to health avoidance until the severity of symptoms necessitates hospitalization. These findings signify a silent public health burden.

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Dedication

This research is dedicated to Dr Andra James (Duke University) and Dr Paula James (Queen's University) for the guidance and insights that shaped the research project.

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I want to acknowledge my former chair Dr. Shinga Feresu, current chair Dr. Hadi Danawi, committee member Dr Simone Salandy and university reviewer Dr Mehdi Agha for their thoughtful feedback and academic guidance throughout this research project.

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Chapter 1: Introduction to the Study

Introduction

Menorrhagia, or heavy menstrual bleeding (HMB), represents the most common gynecological presentation in women of reproductive age (Davis & Kadir, 2017). Consultation with specialist care characterizes ideal healthcare. Individuals lacking health care (insurance) access, who live in remote or rural areas, or who do not understand the potential long-term consequences may then use other healthcare sources, such as the emergency department (ED). Excessive or heavy bleeding has historically been defined as a daily blood loss of greater than 80 mL per menstrual cycle (Hallberg & Nilsson, 1964). This criterion, while measurable, is extremely difficult and impractical to quantify in clinical practice or an ambulatory setting. This quantification measure makes the estimation of HMB somewhat subjective and dependent on the history provided by the patient. The health impact attributed to HMB may affect several aspects of a woman's life. Negative impacts on a woman's overall quality of life (QoL) have been observed (Weisberg et al., 2016). Key aspects including overall mood, level of energy, productivity at work and school, social interactions, daily family life, and sexual functioning are often negatively affected (Hasselrot et al., 2018). The association between blood loss and QoL appears to be directly related (Bruinvels et al., 2016). Women who thus present in the ED may believe that their problem can only be treated in an ED (Dyne & Miller, 2019). Repeated ER visits and hospital admission may represent more severe forms of HMB or reflect other health characteristics (Birmingham et al., 2017). However, the characteristics of women who use the ED for HMB are not well described in the literature.

Estimates of prevalence vary. Life stage characteristics such as parity have not been frequently studied (Rocha et al., 2018). In the United Kingdom, 5% of women aged between 30 and 49 years consult their primary care physician each year with HMB (Davis & Kadir, 2017). However, the health impact of HMB may be substantive. Fraser et al. (2015) reported on reproductive health in a European-wide internet-based population survey conducted in five representative European countries among 4,506 women (aged 18–57 years). They found that two or more HMB symptoms were reported in 1,225 (27%) of the women (Fraser et al., 2015). Within this cohort, 661 (27%) of the women sought medical attention at least once a year (Fraser et al., 2015). Iron deficiency-associated symptoms were frequent, and previous confirmed diagnosis or treatment for iron deficiency anemia occurred in 63% of the women surveyed (Fraser et al., 2015).

Fraser et al. (2015) reported a frequency of HMB within the community of between 30 to 40%. They also observed that age appears to be important, with younger populations reporting slightly higher rates (Fraser et al., 2015). A prevalence rate of 40% was reported in an adolescent population of women aged 12 to 18 (Rocheleau et al., 2017). In a community-based cross-sectional descriptive survey on a randomized sample of the Swedish general population, investigators found a prevalence rate of 32% of women experiencing HMB (Karlsson et al., 2014). This study included an older cohort of 1,547 women, aged 40 to 45 years old. In addition to HMB, they reported that in general, menstrual bleeding was associated with negative perceptions and limited social and professional activities (Karlsson et al., 2014). These negative perceptions affected several QoL domains, especially body pain ($p < 0.0001$) in the Short Form-36v2 (SF-36). These health-related quality of life (HRQoL) scores were significantly more affected in women experiencing HMB than those with normal menstrual bleeding patterns (Karlsson et al., 2014). The Short Form-36v2 SF-36 showed that women experiencing HMB had significantly worse HRQoL compared with women with normal menstrual bleeding in all domains (Karlsson et al., 2014).

Among health indicators of importance, HMB is recognized as a problem suspected to be underreported (Hacioglu et al., 2016). Excessive menstrual bleeding is often difficult to quantify and assess (Gursel et al., 2014). Menorrhagia is thus often characterized as an unexplained bleeding event. These sentinel events of reproductive health may consequently serve as a predictor and surrogate marker of an underlying defect such as an undetected bleeding disorder or platelet defect (Rajpurkar et al., 2016). In early reproductive life, unattended bleeding disorders may have a profound effect on health and well-being (Dowlut-McElroy et al., 2015). Understanding the incidence and characterizing risk factors associated with these events may lead to improved public health awareness of women's health needs in the community.

The impact of HMB on health status and QoL may fluctuate during reproductive years. In the United States, hysterectomy before age 60 occurs in one-third of women (Whiteman et al., 2008). Heavy bleeding associated with uterine leiomyoma, endometriosis, and uterine prolapse is the most common associated symptom. A retrospective 2003 study of inpatient admissions included 300,359 women who were hospitalized for excessive bleeding symptoms had a mean age of 42 years (Morrison et al., 2008). Women between 25 to 50 years represented 85% of the study population. Adolescents, who were defined as women between 12 to 24 years of age, contributed 2% of the study cohort. These women in the youngest age group were 7.25 times ($p < 0.001$) more likely to present with anemia versus not. Additionally, African American and Hispanic women had disproportionate anemia frequencies versus White women (Morrison et al., 2008). Overall, 25% of the in-patient women had anemia.

A global survey of 1,032 health care providers revealed that 61% of women with HMB had no causal coagulopathy (Rocha et al., 2018). These trends support the hypothesis that many women do not appreciate the consequences of excessive menstrual bleeding and most likely do not seek help before this event, leading to health consequences. Additionally, in public health, the role of place is recognized as important. Finkelstein et al. (2017) found that differences in where Medicare enrollees reported their diagnoses to occur reflect not only differences in their diagnosis but differences in the quality of their underlying health. Understanding the association between proximity to the ED and severity of symptoms (captured by admission rates) may estimate disparities with the population.

Understanding the risk factors, comorbidities, and spatial factors associated with ED menorrhagia events have not been assessed in a population setting. Unattended excess bleeding events during reproductive years may lead to a reduced general QoL and lower psychosocial wellbeing (Philipp et al., 2011). Chronic blood loss can lead to an anemic state. Left unrecognized and untreated, anemia may compound QoL decrement by contributing to poor school performance, increased rates of absence from school, and avoidance of physical activity (Kassebaum et al., 2014). Excess days lost from work, lifestyle disruptions, and increased health care costs have also been described (James et al., 2006). Recognition of HMB in early reproductive life may reduce the associated health-related consequences and potentially allow for the management of modifiable contributing factors. Presentation of such events is suspected to take place in EDs (Livesey et al., 2016). To date, no researchers have described the risk characteristics of women in the community who seek attention in the ED for HMB (Rocha et al., 2018). Identifying comorbidities, risks, the contribution of insurance status, and location is not well described Therefore, there is a gap in knowledge of demographic data, comorbidities, and proximity to health care. In this study, I focused on the problem of HMB risk factors not associated with a coagulation defect to address this gap.

Problem Statement

Menorrhagia, or HMB, represents the most common gynecological presentation in women of reproductive age (Davis & Kadir, 2017). Consultation with specialist care represents ideal healthcare (Kiran et al., 2018). Individuals lacking health care (insurance) access, who live in remote or rural areas, or who do not understand the potential long term consequences may then use other urgent healthcare access such as the ED (Sardo et al., 2016). Excessive or heavy bleeding has historically been defined as a daily blood loss of greater than 80 mL per menstrual cycle (Hallberg & Nilsson, 1964). This criterion, while measurable, is extremely difficult to quantify in practice (Quinn & Higham, 2016). This quantification measure makes the estimation of HMB somewhat subjective and dependent on the history provided by the patient (Herman et al., 2016). The health impact attributed to HMB may affect several aspects of a woman's life (Karlsson et al., 2014). Negative impacts on a woman's overall QoL have been observed (Weisberg et al., 2016). Key aspects including overall mood, level of energy, productivity at work and school, social interactions, daily family life, and sexual functioning are often negatively affected (Hasselrot et al., 2018). The association between blood loss and QoL appears to be directly related (Bruinvels et al., 2016). Women who thus present in the ED may be demonstrating certain health-seeking behavior and believe their problem can only be treated in an ED (Rocha et al., 2018). Repeated ER visits and hospital admission may represent more severe forms of HMB or reflect other health characteristics (Birmingham, et al., 2017). The characteristics of women who use the ED for HMB are not well described in the literature.

Estimates of HMB prevalence vary. Life stage characteristics such as parity have not been frequently studied (Rocha et al., 2018). In the United Kingdom, 5% of women aged between 30 and 49 years consult their primary care physician each year with HMB (Davis & Kadir, 2017). The health impact of HMB may be substantive. Fraser et al. (2015) reported on reproductive health in a European-wide internet-based population survey conducted in five representative European countries among 4,506 women (aged 18–57 years). They found that two or more HMB symptoms were reported in 1,225 (27%) of the women (Fraser et al., 2015). Within this cohort, 661 (27%) of the women sought medical attention at least once a year (Fraser et al., 2015). Iron deficiency associated symptoms were frequent; previous confirmed diagnosis or treatment for iron deficiency anemia occurred in 63% of the women surveyed (Fraser et al., 2015).

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Understanding the economic risk factors, potential comorbidities, and location factors associated with ED menorrhagia events have not been assessed in a large population setting. Unattended excess bleeding events during reproductive years may lead to reduced general QoL and lower psychosocial wellbeing (Philipp et al., 2011). Chronic blood loss can lead to an anemic state. Left unrecognized and untreated, anemia may compound QoL decrement by contributing to poor school performance, increased rates of absence from work or school, and avoidance of physical activity (Kassebaum et al., 2014). Excess days lost from work, lifestyle disruptions, and increased health care costs have also been described (James et al., 2006). Recognition of HMB in early reproductive life may reduce the associated health-related consequences and potentially allow for the management of modifiable contributing factors. Presentation of such events is suspected to take place in EDs (Livesey et al., 2016). To date, no researchers have described the risk characteristics of women in the community who seek attention in the ED for HMB (Rocha et al., 2018). Identifying comorbidities, risks, the contribution of insurance status, and location is not known. Therefore, there is a gap in knowledge of demographic data, comorbidities, and proximity to health care. In this study, I focused on the problem of HMB risk factors not associated with a coagulation defect to address this gap.

Purpose of the Study

Increased gains in population longevity in developed nations have shifted the focus of public health from communicable disease mortality to morbidity concerns. The concept of adding life to years versus years to life now is of equal importance (Teutsch & Fielding, 2013). Public health research today needs to be concerned with morbidity reduction, functional capacity gains, and disparity reduction. HMB that is ignored or misdiagnosed for a prolonged duration may contribute to preventable morbidity. The consequences of menorrhagia include anemia, chronic fatigue, and decreased psychosocial wellbeing (Kassebaum et al., 2014). EDs are often the first point of medical contact and may function as a health sanctuary for those with limited healthcare access or for those who have ignored bleeding symptoms (Livesey et al., 2016). ED presentation for menorrhagia may indicate that an individual has exceeded a tolerance threshold (Sriprasert et al., 2017). Those without access to gynecological services may be at increased risk for secondary health issues. Characterizing the incidence and risk factors for women who present at the ED with HMB symptoms is not well known. Quantifying risk factors associated with presentation, including race, age, comorbidities such as diabetes, hypertension, or metabolic challenges remain unexplored. Additionally, hospital admission rates could further help quantify the severity of inadequate care suspected to be the result of limited access to gynecological attention (Demers et al., 2006).

Research Questions and Hypotheses

In this project, I tested the hypothesis that disparities may exist within the community for women who experience HMB. ED presentation for HMB may indicate that an individual has exceeded a tolerance threshold (Sriprasert et al., 2017). A consequence of delayed medical attention may be an increased risk for secondary health issues and reduced QoL. Characterizing the incidence and risk factors for women who present at the ED with HMB symptoms is not well known. Quantifying risk factors associated with presentation, including race, age, comorbidities such as diabetes, hypertension, or metabolic challenges, remain unexplored.

The research questions (RQ) in this study were as follows:

RQ1: What is the association between demographic (age), health status (anemia), insurance status, and ED presentation for HMB?

$H_0$1: There is no statistically significant association between demographic factors (age), health status (anemia) insurance status, and presentation to the emergency room for women of reproductive age in the United States.

H_a1: There is a statistically significant association between demographic factors (age), health status (anemia) insurance status, and presentation to the emergency room for women of reproductive age in the United States.

RQ2: What is the association between health factors (comorbidities such as diabetes and hypertension), admission for menorrhagia, and ED presentation for HMB?

$H_0$2: There is no association between health factors (comorbidities such as diabetes and hypertension) and presentation to the emergency room for women of reproductive age in the 37 states participating in the Nationwide Emergency Department Sample (NEDS) in the United States.

H_a2: There is an association between health factors (comorbidities such as diabetes and hypertension) and presentation to the emergency room for women of reproductive age in the 37 states participating in the NEDS in the United States.

RQ3: What is the association between location and economic status (see Song et al. 2010) and ED presentation for HMB?

$H_0$3: There is no association between location and economic status and presentation to the emergency room for women of reproductive age in the United States.

H_a3: There is an association between location and economic status and presentation to the emergency room for women of reproductive age in the United States.

Theoretical Framework for the Study

The framework for this research is the theory of reasoned action (TRA). Fishbein and Ajzen (1975) proposed the TRA. They postulated that an essential predictor of behavior (i.e., what a person actually does) is their behavioral intention (i.e., a person's intention to perform or not perform the behavior) (Fishbein & Azjen, 1975). Behavioral intention can be considered a joint function of a person's approach toward performing the behavior and subjective norms (Didarloo et al., 2012). Seeking attention for HMB depends on both the attitude of the health-seeking individual and the influence of what they perceive to be normal bleeding. The TRA would thus predict that seeking medical attention at the ED is driven by a perception of a health crisis (see Glanz et al., 2008). The TRA highlights the prominence of intention as a determinant of behavior. Contributing to intention is the individual attitude towards the health issue and the perception of what constitutes normal menses. In the setting of HMB, individual determination of heavy menses patterns that constitute a clinically defined excessive bleeding pattern is theorized to be complex. If an individual relies on a direct relative for bleeding pattern context, they potentially run the risk of referencing a family member who may express the same phenotype and who may also not demonstrate a health-seeking behavior. Thus, a comparison of this health status indicator against an individual from the same genetic pedigree (related family member) results in a biased reference discordant from normal (see Kujovich, 2005). The TRA postulates that perceptual awareness and action are independent determinants of behavioral intention. Individuals who seek medical attention from the ED may be displaying health-seeking behaviors and be recognizing that their menstrual bleeding patterns deviate from a perceptual norm (Roberto et al., 2011). ED presentation would thus suggest that the unattended bleeding patterns are serious in nature and that the woman is exhibiting a concern for personal well-being.

Nature of the Study

Understanding the determinants of menorrhagia and unexplained bleeding requires an in-depth knowledge of the complex interactions of genomic, biological, clinical, lifestyle, and societal factors (Lauer, 2012). Cohort studies have helped researchers to better understand the complex etiology of many diseases, such as cancer and cardiovascular disease (Kennedy et al., 2016). Such approaches have allowed epidemiologists to develop risk prediction analyses and models to improve public health guidelines for prevention and provide evidence for health policies.

Evidence supports the theory that HMB may be associated with negative perceptions and reduced social and professional activities (Karlsson et al., 2014). This impact on health-related QoL may have an enduring effect (Weisberg et al., 2016). Women in the later phases of reproductive life have reported significant reductions in HRQoL (El-Nashar et al., 2010). QoL assessment by the generic SF-36 v2 tool revealed that all domains were significantly more affected in women experiencing HMB versus those experiencing normal menstrual bleeding patterns. In a cohort of 1,547 Swedish women, aged 40 to 45 years old, one-third (32%) were classified as having HMB (Karlsson et al., 2014). This would suggest that the prevalence and impact on overall health in the general population might be underappreciated.

This was a retrospective quantitative study. Binary (or binomial) logistic regression was used. This method is a form of regression used when the dependent variable is a dichotomy and the independent variables are of any type. Employing generalized linear modeling allowed the creation of a regression model with any distribution of the dependent (e.g., binomial, multinomial, ordinal) and any link function (e.g., log for log-linear analysis, logit for binary or multinomial logistic analysis, cumulative logit for ordinal logistic analysis; see Forthofer et al., 2007). Logistic regression can be used to predict a categorical dependent variable based on continuous and/or categorical independents to determine the effect size of the independent variables on the dependent, to rank the relative importance of independents, to assess interaction effects, and to understand the impact of covariate control variables. The impact of predictor variables is usually explained in terms of odds ratios.

Definitions

Women of reproductive age with the diagnosis of HMB were included in the study sample. Women below the age of 10 and above 65 were excluded on the basis that excessive uterine bleeding is due to causes other than those associated with reproductive functioning (see Herman et al., 2016). HMB was defined by the International Classification of Diseases (ICD) code recorded on admission. This is a patient-reported event that may be prone to patient bias. The reliability of self-reported HMB is accepted in the literature, as direct quantification is both time consuming (days) and unrealistic in practice (Davis & Kadir, 2017). Coded events were thus assumed reflective of excessive bleeding.

Log-linear regression models were created to assess risk for severe morbidity with risk ratios and associated 95% CI as measures of effect. Several independent (predictor) variables were assessed. These variables were part of the patient record, and their definitions were expected to be reliable. The reporting of race had challenges. Ethnicity and race are used interchangeably in population research. These terms incorporate several important factors, including linguistic, cultural, biological, and geopolitical factors (Sankar & Cho, 2002). Thus, race and ethnicity, while potentially synonymous, may be interpreted differently. Despite the interest in race, race was self-reported and referred to the woman's person's physical appearance, such as skin, color and eye color (see Mersha & Abebe, 2015). As ascertaining ancestral background was not possible in this study, racial classification, when available, was assumed to reflect each woman's preferred racial identity (Cooper et al., 2018).

Women aged 10 to 64 years with a diagnosis of HMB (metrorrhagia, menometrorrhagia, and polymenorrhoea) were included in the analysis. The first exposure (RQ1) evaluated self-reported demographic variables: age (<19, 20-29, 30-39, 40-49, 50-59, and >60 years of age), health status (anemia), insurance status (Medicare, Medicaid, private, uninsured, or other), income for zip code (ZIP code income quartile), and patient residence (large central metro, large fringe metro [suburbs], medium and small metro, micropolitan and noncore [rural], plus missing). The second exposure (RQ2) assessed the presence of health-related factors, including diabetes and hypertension. Severity of presentation was dichotomized as admission to hospital or not, and if a subject received a transfusion or not. The third association (RQ3) evaluated the patient location and economic status. The national readmissions database (NRD) database captured NEDS subjects who were subsequently admitted to hospital.

Assumptions

Large population studies with HMB have not been performed to date. Stratification and quantification of risk factor association also remain poorly described or unknown. Recent literature has supported the premise that unexplained menstrual bleeding may be a poorly appreciated event. The secondary data collected from ED presentation was theorized to represent the population who has either experienced chronic bleeding patterns that finally trigger a behavioral change or an acute event that triggered concern and the need for rapid attention. The collected case reports did not distinguish between these two histories. A surrogate marker of prolonged bleeding history is the presence of anemia (Nelson & Ritchie, 2015). This marker was used as part of a severity index. The severity of HMB was assumed via two dimensions, hospital admission and receiving anemia therapy, including a transfusion.

The primary outcome of this research project is the characterization of risk factors associated with ED presentation for HMB. Increasing HMB severity is theorized to represent poor health-seeking behaviors. An important determinant includes access to health care. The type of insurance or absence was assumed to represent a partial marker of socioeconomic and financial status, including employment. While insurance status as a socioeconomic measure is limited in robustness, an absence was assumed to reflect unemployment or minimal income attainment.

Scope and Delimitations

In this research, I attempted to identify characteristics and comorbidities associated with HMB presentation in the ED. Exploring location and socioeconomic determinants may also provide evidence for disparities in the community. National estimates were generated from the secondary data, which helped frame the scope of any disparities identified. I did not explore an association between exposure and HMB. Confounding by extraneous effects such as age and other factors was stratified and adjusted for. Confounding by indication and severity was addressed. The presence of associated symptoms (indication) was the selection criterion for inclusion. The severity of symptoms represented a stratum that the ICD codes were not able to categorize. In this study, I used the criterion of hospital admission as a surrogate for either severe symptoms requiring additional complex management or a compromised health state that required additional support. In either case, hospital admission from the ED was classified as a severe health state.

The generalizability of the findings will be established from the study population. The primary concern was how representative the sample was. Subjects who seek attention in the ED are theorized to have severe symptoms, prompting health-seeking action. This population may not be representative of individuals who have access to gynecological care and would thus be managed in a physician’s office. The secondary databases assessed did not capture such visits. These HMB visits collected in the admission and hospitalization databases were limited to those seeking attention in an ED.

The study sample thus represented the more serious or troublesome conditions and not the mild conditions.

Limitations

An important limitation and threat to validity are using data for research purposes for which they are not specifically generated (Kuriyama et al., 2017). Secondary data collected from external sources have this inherent limitation. The data used were dependent on the rigor and accuracy of the collection methods. There were limited options to ensure inaccuracies. One check was on gender. Men reported to be diagnosed with HMB were excluded, as well as the use of age boundaries to exclude exceptional medical conditions. A central element of the validity of these research findings was the accuracy of the disease status. Electronic records in HCUP that use on a categorical code such as the ICD-10-CM/PCS or ICD-9CM are reliable. Studies that have compared diagnoses and procedures reported in administrative data compared with medical records have found acceptable levels of agreement (Casey et al., 2016). With secondary data, the finding should lead to further hypothesis generation that should be prospectively tested with primary data studies.

Significance

Due to the periodic hemostatic challenge of menses, women are particularly susceptible to the effects of a hemostatic defect and are consequently more frequently identified through the presentation of heavy bleeding symptoms (Kujovich, 2005). Women of reproductive age are expected to carry a disproportionate health burden. During reproductive years, menorrhagia that is left untreated may lead to an avoidable health burden (Clark & Cooper, 2016). Unrecognized anemia may contribute to poor educational attainment (Stauder et al., 2018). An additional consequence is an elevated risk for postpartum hemorrhage (James et al., 2011).

This research was designed to characterize the incidence of menorrhagia events and explore potential associated risk factors in a population study. Such community information is not available. Menorrhagia may be due to multiple causes, including hormonal imbalances (Moon et al., 2017), pathological conditions (Brenner, 1996), and hemostatic defects (Dilley et al., 2001). The likelihood of definitive diagnosis in the ED is low, and outcomes associated with ED presentation are mixed.

This public health burden may be responsive to improvements in incidence estimation and risk characterization. The potential findings may contribute to social change in several ways. Social change in its most complete form has several dimensions. It promotes equity, social justice, self-knowledge, service, and collaboration (Read et al., 2016). This research contributes to the risk estimation and characterization of heavy menstrual disease in women who use the ED for their health care.

Summary

Women's health challenges are often underappreciated in public health. Characterization of comorbidities and risk factors associated with HMB when presented in the ER may increase awareness and stimulate improvements in care. Understanding factors that contribute to hospital admission may be both medically end economically important. A goal of this project is to provide evidence that can lead to a reduction of the health burden of women experiencing HMB.

Chapter 2: Literature Review

Introduction

In a systematic review of the literature, I identified gaps in the setting where women present to health care providers, the duration of HMB before being presentation, and the presence of comorbidities that may contribute to risk for bleeding events. HMB is a frequently occurring event that is estimated to affect one-quarter of women of reproductive age (Kiran et al., 2018). Such a high prevalence in the community would suggest that a considerable health burden exists within the population. In the United Kingdom, 5% of women between ages 30 and 49 years consult their primary practitioner annually for HMB (Cooper et al., 2014). These consultations result in approximately one-third of all gynecology referrals (Davis & Kadir, 2017). However, there is significant regional variation in outcomes and surgical management resulting from these referrals (Sayburn, 2014). These findings support the theory that health-seeking behaviors combined with local health provider resources may be important determinants of healthcare outcomes and general well-being during reproductive years.

Literature Search Strategy

I conducted an on-going weekly literature search using MEDLINE (PubMed) and Embase to identify recent original English language articles published in peer-reviewed journals. Recent articles were retrieved and assessed for relevance to the research questions. This does not preclude seminal papers in the field that may have been published beyond a decade ago. The search algorithm was *heavy menstrual disease* AND *menorrhagia* AND *emergency department* OR *adolescent* OR *adult* OR *bleeding disorder* OR *unexplained bleeding*.

Theoretical Foundation

A theory is a collection of interrelated conceptual ideas, descriptions, and schemes to systematically understand events through postulating connections among inputs to either explain observations or predict future events (Brownson et al., 2018). Fishbein and Ajzen (1975) proposed the TRA to potentially reconcile an individual's behavioral intention and their actual actions. This theory proposes that sociodemographic variables are an important determinant in contributing to behavioral intention and action (Esmaeili et al., 2016). The framework theorizes that individual behavioral intention is influenced by a dynamic interaction between beliefs, attitudes, subjective norms, and the value(s) attached to an attribute or behavioral outcome (Evans et al., 2009). The TRA further proposes that individual behavioral choices are composed of the three important dimensions: (a) intention, (b) attitude, and (c) subjective norms (Hansson & Rasmussen 2014). Due to subjective norms and potentially attitude, women who present in the ED because of heavy bleeding symptoms are thus theorized to have delayed health-seeking behaviors. This behavioral action is thus expected to be associated with more profound anemia and related symptoms.

The contributions of subjective norms are theorized to be important. Significant and relevant others are likely to include close family members with a similar genetic pedigree such as mothers, aunts, and sisters. The contribution of subjective norms can be significant. In a study assessing the contributions of TRA components, Roberto et al.

(2011) found a significant association as a behavioral predictor. Using zero-order correlations, the coefficient between social norms and behavioral intention was substantial, $\beta = 0.34$, p $(.26 \leq \beta \leq .42) = .95$. This supports the hypothesis that potentially obvious symptoms could be ignored due to family and subjective norms. Socioeconomic factors may also contribute to household norms that may further compound delays in health-seeking behaviors.

The influence of health perceptions was also expected to be meaningful. A cross-sectional study using convenience sampling of 137 African American adults regarding testing for Hepatitis C found that several dimensions for the TRA contributed to the likelihood of testing being initiated (Rashrash et al., 2017). Several study findings are important. First, there is an increased odd of intention to initiate health-seeking behavior (i.e., to initiate testing for hepatitis C virus) for subjects with higher subjective norms scores (*OR* = 1.42, 95% CI: 1.12–1.79). Also, perceived severity scores (*OR* = 1.39, 95% CI: 1.17–1.65) and perceived benefit scores (*OR* = 1.57, 95% CI: 1.13–2.18) were significant predictors of health initiation behavior (Rashrash et al., 2017). Additionally, individuals who had a previous blood transfusion (*OR* = 8.25, 95% CI: 2.02–33.61) are highly likely to seek testing. This suggests that previous exposure to the health care system is expected to drive behavioral intention.

Using secondary data does not allow for a direct assessment of behavioral intention or subjective norms. This theory was indirectly tested by using surrogate markers for health-seeking behavior and subjective norms. The contribution of sociodemographic variables was also expected to suggest differences in action (see

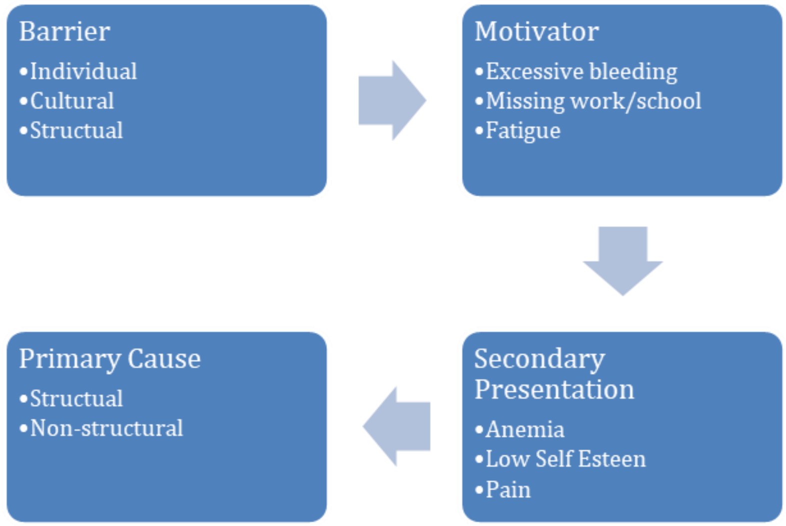
Didarloo et al., 2012). Admission rates from the ED (a severity index)and the presence of severe anemia would indicate a substantial delay in health-seeking behavior. Both intention and subjective norms were expected to contribute to ED presentation. The association between self-efficacy and intention has been shown to be strong (Didarloo et al., 2011). I assumed that individuals are more likely to initiate a health-seeking behavior when their subjective norms delay appropriate attention and conflict with how they feel or perceive their health.

Conceptual Framework

A variety of structural and cultural factors are theorized to act as barriers leading to women with HMB ignoring symptoms until a tipping point is reached. Presentation at the ED represents a reduced health state where attention is being sought. Lee et al. (2014) developed a conceptual framework to address structural and cultural barriers by an ethnic community to health-seeking behaviors. Guided by the TRA, a conceptual framework to this research study was proposed, see Figure 1. Barriers to addressing health needs may include access to primary or specialized health care from inadequate or limited health insurance, rural locations, not having access to academic or specialized care, and low income or socioeconomic limitations. Cultural barriers may include familial phenotypes guiding perceived norms, cultural modesty, and embarrassment as well as the fear of potential causes.

Figure 1

A Conceptual Framework for ED Presentation of HMB.

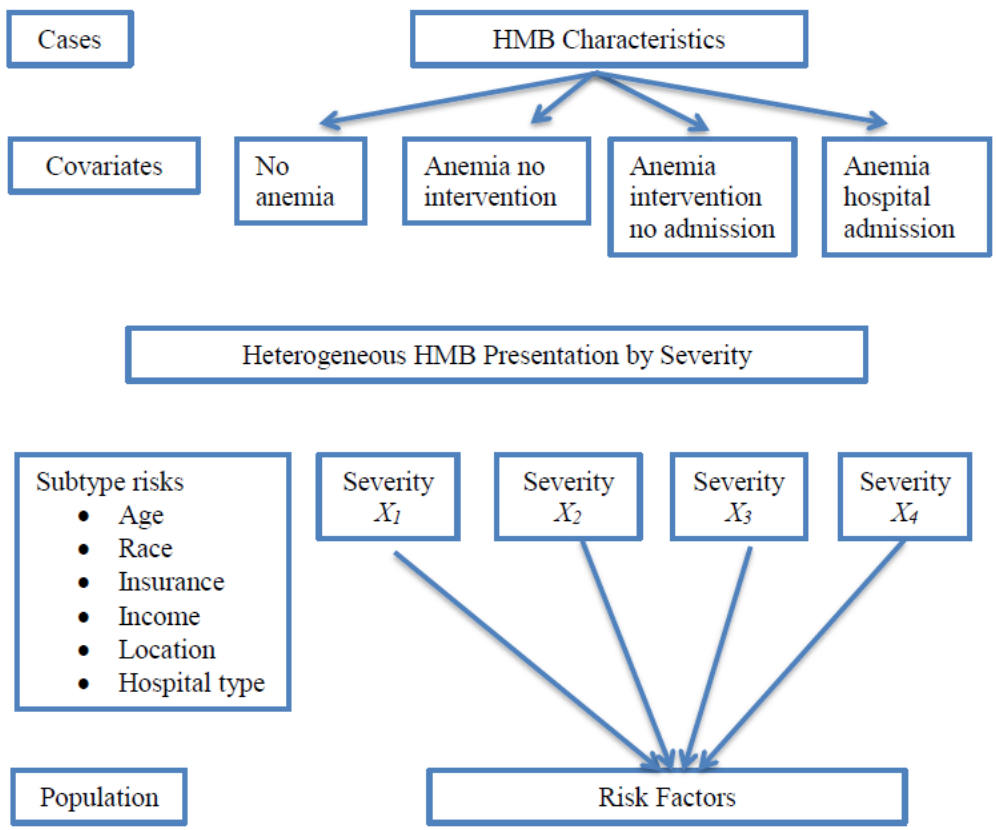


The conceptual framework suggests that characterizing barriers and motivators to seeking health care could potentially lead to a better understanding of who might be at increased risk for HMB. The research findings could guide public health awareness, reduce the likelihood of lifelong burden, as well as update the medical community. A better understanding of who may at increased risk, especially within geographic and socioeconomic groups, provides evidence for the need to reduce disparities. Using this framework supported the research focus of assessing individual comorbidities, demographic characteristics, socioeconomic factors, and place as determinants of HMB risk.

My goal was to determine how to describe HMB severity subtypes that may be distinct. Understanding how ED presentation is influenced by upstream determinants requires a stratification or estimation of severity upon presentation at the hospital and the subsequent health corrective actions initiated. This phenotypic heterogeneity was based necessarily on the concept of risk heterogeneity because risks were expected to vary among different members of the population (see Begg et al., 2013). The severity was defined by the presence or absence of anemia and the corrective steps taken, including admission to the hospital. These severity stratifications were then used to estimate the contribution of predictor (independent) variables to risk, Figure 2.

Figure 2

The Conceptual Interplay of Phenotype and Broad ED Characteristics



Literature Review on Key Variables or Concepts

Menorrhagia or HMB represents the most common gynecological presentation in women of reproductive age (Davis, 2017). Improvements in the health profile of the developed nation's populations during the last several decades have resulted primarily from public health-based changes aimed at the social, dietary, and material environment. These changes have been driven to some extent by improved sanitation and other deliberate public-health interventions (McMichael & Beaglehole, 2000). However, the improvements in longevity in the most developed nations are diminishing. Health care systems are increasingly focusing on reducing morbidity. These efforts have been described as "putting more life in one's years than years in one's life" (Teutsch & Fielding, 2013, p 287).

Health and well-being are complex concepts to define. The impact of chronic blood loss is well documents (Kassebaum, et al., 2014). The National Institute for Health and Care Excellence (NICE), in 2007 defined heavy menstrual bleeding to be the associated consequences of excessive blood loss during menses. The health effect of persistent and frequent HMB episodes is described as a health state which interferes with a woman's physical, emotional, social, and material quality of life, and which can occur alone or in combination with other symptoms (NICE, 2007). An important public health goal is to improve the health of populations (Erwin & Brownson, 2017). To improve health among women with HMB understanding and characterizing risk factors as well as demographic epidemiology will be important. Additionally, the distribution of burden within the community is also not well understood.

When primary care services are not available, alternative options are expected to become necessary. An important alternate health care resource frequently utilized is the emergency department (Sardoet et al., 2016). When women perceive their menstrual flow to be heavy or excessive, they are theorized to be more likely to seek medical care. Evidence shows that women who perceive that their menstrual flow as heavy utilizes more health care resources than women with a light flow, *OR* = 1.45 (95% CI: 1.02-2.05) (Cote et al., 2001). Emergency department utilization was even more pronounced OR 1.79 (95% CI: 1.36-2.37). The most prominent contributors to mortality and morbidity globally and in the United States are behavioral factors (Glanz & Bishop, 2010). Seeking health care for HMB in an ER setting suggests that these women may be a different and varied population within the community. Characterizing comorbidities, the burden of disease, demographics, and socioeconomic indicators such as insurance status may identify public health opportunities to improve outcomes and minimize the health and cost burden associated with HMB.

Menstrual disorders are a substantial reason for obstetric-gynecological consultations (Byams et al., 2012). A common estimation of prevalence is in the range of approximately 30% of women of reproductive age experiencing menorrhagia (Vilos et al., 2001). Menorrhagia or heavy menstrual bleeding (HMB) thus represents the most common gynecological presentation in women of reproductive age (Davis, 2017). This bleeding can have a negative impact on a woman’s quality of life. If left unattended, increased health-related costs and decreased quality of life are two expected consequences of HMB.

Definition of Heavy Menstrual Bleeding

Heavy menstrual bleeding has a historical definition of a daily blood loss of greater than 80 mL per cycle (Hallberg et al., 1966). In practice, the Federation of

Gynecology and Obstetrics (FIGO) classification scheme is now considered more practical and less confusing criteria for defining HMB (Munro et al., 2011). This scheme recognizes other factors including; disturbances in frequency, irregular bleeding, duration beyond eight days, heavy blood loss, and inter-menstrual bleeding episodes. The most challenging aspect of these definitions is the practical difficulties in the quantification of blood loss.

Normal menses should occur every 21–45 days. The bleeding duration is expected to last at least seven days. Pad or tampon use should average 3–6/day (Haamid et al., 2017). HMB is defined as bleeding intervals of more than 7 days with an estimated blood loss exceeding 80 ml per menstrual cycle. Additional symptoms suggestive of HMB may include frequent changing a pad or tampon including time intervals of less than one to two hours. Preventative strategies such as the use of double hygiene protection to reduce the frequency of soiling of clothes or bed sheets have been reported (Nooh et al., 2016). When visualized, blood clots greater than one inch in diameter and effects of quality of life have noted (Moon et al., 2017). These observations have helped clinicians frame diagnostic conversations to be focused on measurable and quantifiable elements of HMB.

Most clinical presentations of HMB are based on self-reported perceptions. Patient-reported concerns may be subjective and prone to bias. A retrospective analysis of a large U.S. medical claims database identified 34,941 women diagnosed with HMB (Copher et al., 2013). These women were insured and had pharmacy benefits indicating access to health care. Almost three-quarters of the women who had an underlying disorder were over 40 years of age versus 55% of the women who were classified as idiopathic. When the study cohort was classified by age, a trend of increasing proportion by age was noted. The youngest age cohort aged 18 to 34 years represented 16% of the study population. The next older cohort 35-39 years represented 21% of the population while the oldest cohort age 40 to 49 years was 63%. The trend supports the theory that with or without underlying causes HMB burden to healthcare systems appears to increase over with age. Women appear to become more self-aware of their health status as they age and with access to the care they may seek medical attention more readily. Beyond this study are the consequences and burden of disease in women without healthcare access.

Causes

Several causes should be suspected when HMB presentation occurs. Causes are multifactorial. Heavy menstrual bleeding may result from several sources. Gynecologic, systemic, or iatrogenic causes should be suspected (Brenner, 1996). Half of the cases are attributed to defects of the coagulation system (Dilley, et al., 2001). The remaining half does not have an identifiable cause. Among coagulation defects, platelet disorders (Rocheleau, et al., 2017), Bernard Soulier syndrome, and underlying bleeding disorders such as von Willebrand disease (VWD) and low levels of FVIII, FIX, FX are common causes (James, et al., 2011). For coagulation defects, several bleeding history events should suggest suspicion, see Table 1.

Table 1

Sentinel Events for a Coagulopathy

Bleeding history events that should arouse suspicion of a coagulation defect
Prolonged bleeding from trivial wounds lasting >15 min
Heavy, prolonged, or recurrent bleeding after surgery
Heavy, prolonged, or recurrent bleeding after dental procedures such as a tooth extraction
Bruising with minimal or no trauma, especially resulting in a lump 1–2 times/month
Nose bleeds lasting >10 min or requiring medical attention 1–2 times/month
Unexplained gastrointestinal tract bleeding
Anemia requiring corrective iron therapy or transfusions
Heavy menstrual bleeding
Family history of bleeding disorders such as von Willebrand disease or hemophilia
Family history of hysterectomy at a young age
Postpartum hemorrhage

Adapted from Haamid, Sass, and Dietrich, 2017

Table 2

Differential Diagnosis for Heavy Menstrual Bleeding

Differential diagnosis of heavy menstrual bleeding
Endocrine
Anovulatory bleeding
Polycystic ovary syndrome
Thyroid disease
Bleeding disorders
von Willebrand disease
Platelet dysfunction
Thrombocytopenia
Clotting factor deficiency
Infection
Sexually transmitted infections
Cervicitis
Endometritis
Pregnancy
Abortion
Ectopic pregnancy
First trimester bleeding
Gestational trophoblastic disease

Postpartum bleeding
Medication
Anticoagulants
Depot medroxyprogesterone
Intrauterine Device
Uterine
Leiomyoma
Polyp
Aenomyosis
Malignancy
Other
Trauma
Foreign body
Hemorrhagic ovarian cysts

Adapted from Moon, Perez-Milicua, & Dietrich, 2017

Classification

HMB is classified by the International Federation of Gynecology and Obstetrics as either structural of non-structural (Munro et al., 2011). This system uses the acronym PALM-COEIN, see table 3. HMB is classified as either structural or non-structural. Many cases of HMB present as secondary to other conditions. Approximately 50% of cases are idiopathic where no known cause is identified (Byams et al., 2012). Circumstances, where cause cannot be established, can be expected to lead to treatments focused on symptoms versus cause.

Table 3

Classification System for Causes of Abnormal Uterine Bleeding in Nongravid Women of Reproductive Age

PALM: Structural causes	Polyp abnormal uterine bleeding (AUB)	
	Adenomyosis AUB	
	Leiomyoma AUB-L	Submucosal Other
	Malignancy and hyperplasia AUB	
COEIN: Nonstructural causes	Coagulopathy AUB	
	Ovulatory dysfunction AUB	
	Endometrial AUB	
	Iatrogenic AUB	
	Not yet classified AUB	

Adapted from Moon, et al., 2017

Prevalence Estimates

Estimates of prevalence vary. When HMB blood loss is objectively measured prevalence rates range between 9 and 14% (Chodankar et al., 2018). When subjective assessments are studied the prevalence rates reported are between 20 and 52% (Clark, 2016). Discordant prevalence estimates between objective and subjective patient-reported approximations suggests a gap in perception of health exists. Several factors may contribute. Life stage characteristics such as parity are not frequently studied. In the UK, 5% of women aged between 30 and 49 years consult their primary care physician each year with HMB (Davis, & Kadir, 2017). The annual UK cost associated with the 1.5 million primary consultations for menstrual complaints exceeds £65 million (Chodankar et al., 2018). Thus HMB frequency estimates in the 20 to 30% range appear to be supported by care-seeking frequency and health care cost burden data.

Community sampling may best accomplish assessing population prevalence. A European wide internet-based survey conducted in five European countries among women (aged 18–57 years) surveyed 4506 women. Two or more HMB symptoms were reported in 1225 (27%) of the women. Within the cohort, 661 (27%) of the women sought medical attention at least once a year. Iron deficiency-associated symptoms were frequent, previous confirmed diagnosis or treatment for iron deficiency anemia occurred in 63% of the womgen surveyed (Fraser, et al., 2015). There could be bias because the present study was based only on women's perceptions. The strong association with iron deficiency would be consistent with expected pathophysiology and be a meaningful surrogate for disease burden estimation.

Several reports suggest a frequency within the community of between 30 to 40%. Age appears to be important, with younger populations reporting slightly higher rates. A prevalence rate of 40% was reported in an adolescent population of women age 12 to 18 (Rocheleau, et al., 2017). In a community-based cross-sectional descriptive survey on a randomized sample of the Swedish general population, investigators found a prevalence rate of 32% of women experiencing heavy menstrual bleeding (Karlsson et al., 2014). This study included an older cohort of 1547 women, aged 40–45 years old. In addition to HMB they also reported that in general, menstrual bleeding was associated with negative perceptions and limited social and professional activities. These negative perceptions affected several quality of life domains in the Short Form-36v2 SF-36. These health-related quality of life (HRQoL) scores were significantly more affected in women experiencing heavy menstrual bleeding than those with normal menstrual bleeding patterns. The Short Form-36v2 SF-36 showed that women experiencing heavy menstrual bleeding had significantly worse HRQoL compared with women with normal menstrual bleeding in all domains.

Anemia

Anemia is characterized by several distinguishing features that manifest via altered erythrocyte morphology. A classic presentation of includes reduced red blood cell quantity, low hemoglobin levels, or transformed red blood cell morphology (Kassebuam et al., 2014). Surveillance of anemia is challenging. Iron deficiency is the most common micronutrient deficiency worldwide (Percy, & Mansour, 2017). Globally iron deficiency anemia (IDA) prevalence is estimated to be approximately 29% among non-pregnant women between ages 15 to 49 (Bernardi et al., 2016). This evidence suggests that IDA is a common problem that may be a consequence of other health-related determinants. Frequent blood loss due to heavy bleeding is expected to be an important health status determinant.

There are several initiating factors associated with the development of iron-deficient anemia. IDA is influenced by low socioeconomic status, low body weight, and in females who have recently given birth (Kassebaum, et al., 2014). Inadequate dietary iron such as a vegetarian diet and chronic blood loss are known causes of anemia (Chen, Chao, Cheng, Hu, & Liu, 2008). Most cases of anemia develop over decades which may facilitate slow recognition or adaptation to the associated health effects. The downstream consequences of unattended anemia may have a substantial impact on an individual’s life. Reduced oxygen-carrying capacity can affect multiple organ systems.

The association between age and anemia in women is complex. In early life before puberty 3.6% of children under age five are anemic (Friedman et al. 2012). During adolescence, the rates increase due to growth spurts, menstrual blood loss, and dietary issues. Pregnancy adds additional demand to iron needs. IDA develops in 37% of pregnancies among US women (US Preventive Services Task Force, 1993). In the peri-menopausal period, an estimated 13% to 20% of women suffer from anemia primarily due to excessive blood loss. After reproductive years anemia becomes less prevalent. A constant concern regardless of life stage is the health impact associated with anemia.

Iron deficient anemia left uncorrected may cause many symptoms related to poor health. The reduction in red cell volume may lead to outcomes due to impaired tissue oxygen delivery. Decreased cognitive performance has been associated with IDA. During formative years mental and motor skills may be affected (McCann, & Ames, 2007). Women or reproductive age may experience symptoms such as weakness, fatigue, difficulty concentrating, or poor work productivity (Haas, 1986). The susceptibility of several important health systems to IDA reinforces the importance of recognizing risk factors that contribute to frank anemia especially when a presentation is in an emergency department setting.

Anemia is a global health problem that disproportionally affects women. In the United States, racial disparity has been observed. Analysis of the 1999 – 2002 National Health and Nutrition Examination Survey (NHANES) found persistent differences in the prevalence of iron deficient-anemia among African American and Mexican American women. The prevalence rate among white women was 3.3%, Hispanic was 8.7%, and for black women was 24.4%. The cohort examined was all under age 50 years with a diagnosis of anemia (Cusick, et al., 2008). Factors that may contribute include high rates of parity low socioeconomic status, lower educational attainment, and persistent HMB (Friedman et al. 2012). Understanding the public health burden of HMB should include exploration of effect measure modification presence. Anemia, race, and age may be important modifiers.

Hysterectomy

Abnormal uterine bleeding due to structural causes (PALM) may respond to medical management. The SOGC guidelines recommend preservation of fertility especially in early reproductive life unless otherwise specified (Lefebvre, et al. 2002). Hysterectomy may be indicated for cases of HMB refractory to conservative surgical management or to medical treatment. When leiomyomas are present, management of symptomatic fibroids via hysterectomy provides a durable solution to heavy menstrual bleeding and the symptoms associated with an enlarged uterus. This recommendation received a 1A grade. The option of medical management for other causes of HMB results in the possibility that hysterectomy may be an option that is over-utilized when both structural and non-structural causes are not identified.

After cesarean delivery, hysterectomy is the most frequently performed major surgical procedure for women of reproductive age in the United States. Roughly 600,000 hysterectomies are performed each year in the United States (Whitman et al. 2008). An estimated 20 million US women have had a hysterectomy. By age 60 more than one-third of all women have had a hysterectomy (Whitman et al. 2008). The most common indication for hysterectomy was uterine leiomyoma which includes the broad classification of menstrual disturbances. This indication accounts for 40.7% of all U.S. hysterectomies. In population terms, the rate of hysterectomy for uterine leiomyoma was 2.2 per 1000.

Globally similar trends are observed for hysterectomy. In Denmark, a country with comprehensive medical access, 7,700 women annually undergo elective hysterectomy including laparoscopic hysterectomy for benign indications (Topsoee et al., 2016). This population frequency equates to an estimated 10% lifetime risk for all Danish women. The procedure in Denmark is most commonly performed due to abnormal menstrual bleeding, leiomyomas, descensus of the uterus, or abdominal pain (Nielsen et al., 2011). These utilization trends of hysterectomy support the premise that gynecological care in first world countries for HMB may be similar.

The type of surgical procedure utilized for menorrhagia or leiomyoma appears to differ based on patient characteristics. The less invasive laparoscopic procedure in the US appears to be utilized differentially. A retrospective cohort study analyzing the HCUP Nationwide Inpatient Sample databases found significant differences in the surgical management women received for HMB based on race, gender, and insurance status (Lee, et al. 2014). Examination of 530,154 cases between 2003 and 2010 showed that the likelihood of women with HMB undergoing a laparoscopic hysterectomy remained greatest for women who were under 35 years of age, white race, with high median income defined as above the fourth quartile nationally, and with private insurance. This data would imply that women with HMB who seek elective surgical management receive treatment disparities.

Another important concern is the utilization of hysterectomy for HMB due to non-structural causes. Defects in coagulation pathways such as deficiency of Von Willebrand factor (VWF) would not be expected to be resolved by hysterectomy. Utilization in this situation would expose the woman to unnecessary surgical risks with a low likelihood of success. HMB is a leading indication for hysterectomy, the most common non-obstetric surgical procedure in women in both the United Kingdom and the United States (Harlowa, & Campbell, 2004). The utilization of hysterectomy for idiopathic HMB is lower than for structural causes; however, Copher et al. (2013) reported a rate of 10% among the 21,362 idiopathic cases examined in their study. This unexpectedly high use of surgical management among women who would most likely experience minimal symptom improvement suggests that the burden of HMB may also include costly and risky surgical therapies.

Hospitalizations

HMB is associated with frequent visits to physician offices, emergency departments leading to in many cases hospitalization. Despite medical therapy is an effective option for many women, surgical approaches are often utilized (Winston et al., 1999). Hospitalizations for procedures such as hysterectomy accompanying HMB are common. Analysis of a population-based survey the National Health Interview Survey 1999 found that women with the self-reported heavy menstrual flow were at least 1.45

times more likely to utilize health care services such as hospitals versus matched control women (Côté et al., 2003).

Evidence of disparities exists when hospitalizations are considered. Women with HMB have similar health status comparator women undergoing hysterectomy. However, the lower socioeconomic status appears to be important. Income disadvantage and lower educational attainment are associated with increased exposure to surgical management via hysterectomy and hospitalization (Marshall et al., 2000).

Quality of Life

Excessive menstrual blood loss is estimated to affect up to one-third of women during reproductive years (El-Hemaidi et al., 2007). Perception of reduced energy capacity and activity levels related to work and family are theorized to drive health-seeking behavior. Women who experience HMB will often present to either a primary care physician or an emergency department primarily due to the consequent negative influence on their daily activities (Santer et al., 2007). HMB has been shown to adversely affect several domains important in quality of life (QoL) assessment. A cross-sectional postal survey of 906 women in Scotland by Santer et al. (2007), found that pain was the most frequent complaint followed by heaviness, changes in mood, and fatigue. Consistently reported QoL concerns to include reduced energy vitality, work productivity, social interactions, family life, and sexual functioning (Liu et al., 2007). The primary consequences that HMB has on a woman's health-related quality of life (HRQL) originates from two sources (Lukes et al., 2012). The health-seeking effort associated with managing menstrual bleeding and the downstream consequences of excessive blood loss, including fatigue and iron deficiency anemia.

In adolescent women, the effect of heavy menstrual bleeding on QoL is theorized to be pronounced. Torres, et al. (2017) interviewed 46 adolescents between ages 10 and 18 years. Using the PedsQL 4.0 instrument, they found that the emotional dimensions were most affected. In this cohort, social absences were frequently reported. Frequent absence (at least day per month associated with at least 75% of periods) from school due to HMB occurred in 50% of adolescents, 80.4% missed physical education, and 65.2% limited outdoor activities or parties due to HMB. This study design also included interviews of the subject's parents or guardians. They found that the perceptual impact of HMB was discordant. Parents viewed HMB as a less serious health issue and having a lower activity impact than the adolescents. This evidence would support the premise that the health burden accompanying HMB is often not fully appreciated even by close family members.

The QoL differences between women with HMB and matched controls appear to be significant in several health-related domains. A systematic review of 98 studies supports this premise (Liu et al., 2007). Pooling SF-36 scores, women with HMB had lower SF-36 scores for all eight subscales compared to mage matched American women. The physical role functioning and emotional role functioning subscales were significantly different, see table 4. These two domains assess daily tasks and work productivity functions. The majority of the subscale scores (six of the eight) were below the 25th percentile of the national scores. The most significant difference versus national norms was found in the physical role functioning domain. This difference, 60.3 vs. 83.2, was 23 points below the 25th percentile of the national norms. In most health-related domains women across all ages appear to function well below national norms and best function in the bottom quarter of their age-matched peers.

Table 3

Impact of HMB on QoL: SF-36 Subscale Scores Versus the National Norms

		Physical function	Role/ physical	Pain	General health	Vitality	Social function	Role/ emotional	Mental Health
National norms	25th percentile	83.3	83.2	60.9	64.2	46.2	72.1	70.4	63.6
	Mean	87.5	84.4	76.7	73.8	59.3	83.1	81.1	73.1
HMB	Meta-analysis (random-effects)	82.1	60.3	58.5	69.9	43.9	66.1	62.3	62.4

Note. Max score = 100. Adapted from Liu et al., 2007

The Role of Age

Menstrual bleeding occurs during reproductive years beginning around age 10-12 continuing to peri-menopausal years near age 50. This study will consider HMB across a woman's reproductive lifespan. The health impact during the early years can be substantial. An adolescent population reported that 60% experienced a serious effect on life activities (Esen et al., 2016). In adult years, including peri-menopausal years HMB continues to affect health status and quality of life (Herman et al., 2016). Regardless of age, a women's perception of bleeding severity does not often correlate with the objectively measured blood loss (Gkrozou, et al., 2015). Approximately 40–50% of women who complain of HMB have an excess of 80 ml blood loss which would suggest that the majority do not. This evidence would support the approach of studying and exploring risk factors across reproductive life. The Theory of Reasoned Action would suggest that behavioral intention would change throughout the reproductive years.

Across all age groups, HMB relies on a seldom-used definition of blood loss. Using a meta-ethnography approach Garside, Britten, and Stein (2008) attempted to synthesize health related findings to understand the impact of HMB among women of reproductive age. Estimates that up to 60% of women with normal blood loss present with HMB, including half of those treated surgically, would suggest that understanding the characteristics of these women is important. The converse may also be expected, there is a proportion of women who do not seek help despite having objectively heavy blood loss. Several factors may support the uncertainty about how valid a woman’s subjective experiences may be. These experiences are theorized to affect health-seeking decisions and may change during life course. These can include ambivalence in assessing their periods as problematic (Garside Britten, & Stein, 2008). Several themes emerged from the research. Some women may have an internalized belief that suffering is an essential component of menstrual biology. This belief may be conflated with difficulties in assessing one’s own experience in comparison to that of other women. Thus, changing health-seeking behavior will rely on the validity of their perception of heavy blood loss. Cultural influences may also be important. Women who have the perception that menstrual blood loss, even if heavy, is a necessary cleansing process may avoid seeking help.

The cost burden associated with a presentation to healthcare providers is substantial across all ages. A retrospective analysis using health insurance data of 6,315 Japanese women found that after adjustment for baseline characteristics including age, costs associated were 2.2 times higher in patients initially presenting to a healthcare provider and 2.9 times higher for women with repeated claims (Akiyama et al., 2017). This was significantly greater than matched controls (both $P < 0.0001$). This supports the hypothesis that the health burden increases as symptoms are not addressed.

Economic Burden

The economic burden from a relatively high-frequency health challenge present in a large segment of the population is expected to be substantial. A conservative estimate of annual direct economic costs attributed to HMB suggests that approximately $1 billion is lost annually (Côté et al.,2001). Indirect costs may reach $12 billion annually. These estimates do not account for intangible costs and productivity loss due to reduced vitality or functional capacity. Direct costs can be quantified. Women who reported HMB were more likely to consult a physician (OR = 1.48, $P \leq 0.01$), present at an emergency department (OR = 1.79, $P \leq 0.01$), and to endure a related surgical procedure (OR = 1.56, $P \leq 0.01$) (Shapley et al., 2004). The 150,000 HMB related hysterectomies performed in 2005 represented 25% of the national total and consumed USD 567 million. These demands for direct medical services demonstrate the cost burden associated with HMB.

There are very few studies exploring the impact of HMB on work productivity. Hurskainen et al. (2001) reported that among 226 women with HMB, 20% reported having missed work due to HMB within the previous 6 months. Structural causes such as fibroids may be important. In a large prospective study, Pron et al. (2003) found that 40% of women with fibroids (80% of whom reported heavy menstrual bleeding) reported missing work in the previous 12 months due to fibroids. The duration of lost work time was substantial often involving several days a month. There is a temporal association with the timing of menstruation. Among women requiring surgical management for HMB, 39% to 55% needed to take time off work prior to surgery (Dwyer, Hutton, & Stirrat, 1993). Cote et al. (2001) estimated that women with HMB worked 3.6 weeks fewer per year versus matched controls. They also estimated that this annual work loss duration translates to $1692 annually per woman. The methodology for estimation only took into account actual absenteeism, not reduced productivity due to fatigue and reduced vitality. Thus potential productivity reduction attributable to HMB may have been substantially greater than just counting lost days of work.

Consequences

The consequences of HMB, a high-frequency health challenge present in a large segment of the population require attention. A cross-sectional survey of 225 women with heavy menstrual bleeding provided six important themes related to the consequences of HMB (Chen et al., 2018). From qualitative interviews the authors found (a) Symptomatic experience was very heterogeneous, (2) Symptoms experienced varied across the reproductive life span, (3) Multiple factors influenced HMB symptoms and their health impact, (4) HMB symptoms could adversely affect daily activities, (5) HMB was not perceived by health care providers as a valid health issue, and (6) Treatment for women with HMB varied in satisfactoriness and usefulness. These findings suggest that the term of heavy menstrual bleeding may categorize a broad spectrum of symptoms, health related–challenges, and population burden. Women who experience HMB will often seek medical attention primarily due to the consequent negative impact on their daily lives and activities.

Public Health Concern

Morbidity reduction from the identification of potentially modifiable risk factors should be the product of purpose-driven public health research. HMB is a major problem for a substantial proportion of women of reproductive age. The patient journey is expected to be lengthy and potentially associated with frequent emergency room visits to address outcomes such as pain, excessive bleeding, and anemia. There is strong evidence that women with HMB face a health care bias. A study characterizing the patient journey of 10,354 individuals with a bleeding disorder quantifies the potential bias (Sidonio, et al., 2017). The study focused on individuals who were serially misrecognized. This was defined as those who visited the same specialist type at least twice for an episodic bleed prior to diagnosis. Of the proportion (one quarter) of patients misrecognized, 82% were women. Those in reproductive years (age 16-54) represented 54% of the cohort. The likelihood of being misrecognized was equally distributed among the health care providers that these patients presented to; gynecologists (35%), emergency room/hospitalists (33%), and primary care physicians (33%). Emergency department consultation for HMB symptoms is expected to be the culmination of several health determinates.

Summary and Conclusion

The literature review has identified a substantial burden associated with HMB. Heavy menstrual bleeding is a common health problem (Davis & Kadir, 2017). The Theory of Reasoned Action would predict that women who are uncertain about their bleeding patterns may or may not seek medical advice. Those who are concerned or suspect that their bleeding pattern is heavy do not have an objective assessment option. These women may or may not have a blood loss beyond the 80 mL definition of HMB (Gkrozou, et al., 2015). Those seeking medical assistance in the ED are theorized to represent a cohort who may; a) be secure in the validity of their personal experience, b) have a cultural or supportive environment where they are encouraged to seek help, and c) there may be fear that HMB is a manifestation of other health-related concerns such as cancer. The demographic characteristics and comorbid risk factors across the reproductive life span in women who seek health care in the ED are not well understood.

Women experience an uncertainty about their menstrual bleeding patterns. The question of whether or not their bleeding is abnormal is influenced by their perceptual model. The intention and attitude to seek help in an emergency department are expected to be driven by multiple determinants. When women do initiate health care-seeking behavior for HMB, patients preferred a shared decision approach (Zandstraa, Busserb, Aartsb, & Nieboer, 2017). Additionally, when an intervention was initiated, a women’s pre-visit preference was the strongest predictor for treatment choice. These findings would support the hypothesis of the TRA that subjective norms and health care experience are relevant and influential in health-seeking behavior for HMB. If health service personnel adhere to a strict definition of HMB blood loss, they may ignore relevant phenotypes and bias women to avoid further consultation. Understanding who seeks consultation across the reproductive lifespan will potentially enable improved sensitivity to needs and reduction of lifelong burden.

Chapter 3: Research Method

Introduction

The consequences of protracted HMB include anemia, chronic fatigue, and decreased psychosocial wellbeing (Kassebaum et al., 2014). EDs are often the first point of medical contact and may function as a health sanctuary for those with limited healthcare access or for those who have ignored bleeding symptoms (Livesey et al., 2016). ED presentation for menorrhagia may indicate that an individual has exceeded a tolerance threshold (Sriprasert et al., 2017). Those without access to gynecological services may at increased risk for secondary health issues. Characterizing the incidence and risk factors for women who present at the ED with HMB symptoms is not well known. Quantifying risk factors associated with presentation, including race, age, and comorbidities such as diabetes, hypertension, or metabolic challenges, remains unexplored. Additionally, understanding hospital admission rates could further help quantify the severity of inadequate care suspected to be the result of limited access to gynecological attention (Demers et al., 2006).

To estimate population risk parameters, analysis of large national databases was an ideal approach. The HCUP databases, which are a federal-state-industry partnership in health data, sponsored by the Agency for Healthcare Research and Quality, allowed for meaningful research to address the research questions. This secondary data source of ED admissions contains over 32 million records each year from approximately 1,000 EDs (HCUPnet, 2018). Weighted, this data sample estimates approximately 135 million ED encounters. The NEDS contains discharges from more than 950 hospitals and approximates a 20% stratified sample of U.S. hospital-based EDs. A description of the research design, data sources, and statistical plan follows.

Research Designs and Rationale

In this retrospective quantitative cohort study, I used secondary data collected from the Agency for Healthcare Research and Quality. The study population was derived from ED visits and hospital admissions collected by a stratified systemic random sample from reporting hospitals. The project sample was designed to generate a study population systematically drawn from a list of ED presentations collected. An important advantage of this secondary data source is that the study population could be weighted to be representative of the entire United States across medical specialties and included academic, community, nonfederal, general, and specialty-specific centers, including obstetrics and gynecology (see HCUPnet, 2018).

Logistic regression was used in this research as my aim was to predict whether ED presentation due to HMB results in hospital admission or not, that is, the presence or absence of an event is being sought. The estimated logistic regression coefficients were used to estimate *OR*s for each of the independent variables in the model. The dependent variable in the logistic regression model was the hospital admission, yes or no (dichotomous). Logistic regression methods are appropriate to model data where the dependent variable is dichotomous (Sun et al., 2017). A large sample set was used to assess several risk factors. Seven predictors (independent variables) were explored in the analysis plan, see Table 5.

The use of secondary data to assess risk factors has been effective in identifying risk factors (Morrison et al., 2008). The use of logistic regression in a population with phenotypic heterogeneity has been demonstrated (Begg et al., 2013). The research design and use of logistic regression models allowed me to address the three research questions, which asked about demographic, health, socioeconomic, and spatial associations. Several of the independent variables had multiple categories, which further allowed for the characterization of high-risk individuals within the community.

A standard epidemiologic approach for modeling risk factors of a categorical outcome typically entails fitting a polytomous logistic regression via maximum likelihood estimation (Sun et al., 2017). By limiting the dependent variable to admission or no admission to hospital, heterogeneity within the population was masked. Methods such as factor analysis were used to address this limitation. Factor analysis is appropriate to identify variables that contribute to HMB and describe how each factor's effect may be interpreted (Dmitrienko & D'Agostino, 2018). Understanding risk factors associated with anemia severity provided evidence to support the research focused on women at high risk for poor health outcomes and QoL.

Table 5

Independent (Predictor) Variable Description

Predictor variable (Independent)	Date type	Categories
Age	Continuous	6
Anemia status	Dichotomous	Yes or No
Diabetes status	Dichotomous	Yes or No
Hypertension	Dichotomous	Yes or No
Insurance status	Categorical	5
Income	Categorical	4
Residence location	Categorical	7

Dependent Variable

HMB was dichotomized to either no hospital admission (treat and release) or hospital admission (admission from the ED). Hospital admission was determined from the NRD database. Within the NRD, a hospital admission is recorded regardless of cause, and trauma is excluded. The outcome of hospital admission was cases related to the HMB index event. These were categorized as hospital admission. This was dichotomous, either yes or no. These two states relied on the clinical judgment of symptoms at ED presentation by healthcare providers and any laboratory or diagnostic interventions performed. I assumed that ED presentation severity is a consequence of both underlying pathophysiologies and delayed health-seeking behavior (Figure 1). Severe anemia was expected to be the most profound HMB outcome that leads to hospitalization (Nelson & Ritchie, 2015). The impact of anemia on well-being and health is substantial (Friedman et al., 2012). Admission status is directly measured in the HCUP datasets, via admission records. Construct validity was expected to be highly certain as hospital admission from the ED generates a unique patient billing code. The dichotomous dependent variable, admission status, was thus a surrogate for severe HMB versus non-severe cases.

Research Questions

The research questions were as follows:

RQ1: What is the association between demographic (age), health status (anemia), insurance status, and ED presentation for HMB?

$H_0$1: There is no statistically significant association between demographic factors (age), health status (anemia), insurance status, and presentation to the emergency room for women of reproductive age in the United States.

H_a1: There is a statistically significant association between demographic factors (age), health status (anemia), insurance status, and presentation to the emergency room for women of reproductive age in the United States.

RQ2: What is the association between health factors (comorbidities such as diabetes and hypertension), admission for menorrhagia, and ED presentation for HMB?

$H_0$2: There is no association between health factors (comorbidities such as diabetes and hypertension) and presentation to the emergency room for women of reproductive age in the 30 states participating in the Nationwide Emergency Department Sample (NEDS) in the United States.

H_a2: There is an association between health factors (comorbidities such as diabetes and hypertension) and presentation to the emergency room for women of reproductive age in the 30 states participating in the NEDS in the United States.

RQ3: What is the association between location and economic status (see Song et al. 2010) and ED presentation for HMB?

$H_0$3: There is no association between location and economic status and presentation to the emergency room for women of reproductive age in the United States.

H_a3: There is a association between location and economic status and presentation to the emergency room for women of reproductive age in the United States.

Methodology

The methodology captured ED HMB presentations via the NEDS database and hospital admission events via the NRD. The International Classification of Diseases, 10th revision, Clinical Modification (ICD-10-CM/ PCS) diagnostic codes for metrorrhagia, menometrorrhagia, and polymenorrhoea (N91, N92, N93) respectively were used to create the study population. Because the individual data and source hospitals were both de-identified, the university institutional review board's privacy and patient protection rules was satisfied.

Women of reproductive age with the diagnosis of HMB were included in the study sample. Women under the age of 10 and above 65 were excluded on the basis that excessive uterine bleeding is due to causes other than those associated with reproductive functioning. The upper age boundary was partially determined by the age stratification of the data set. The majority of cases were below age 50. Women have been noted to have HMB in their fifth decade (Hasselrot et al., 2018). Additionally, a check of the 2014 HCUP data set revealed that 16% of HMB cases occurred in the 45 to 64-year age category. The mean age was 48.4 years. Age 65 and older, as expected, had zero cases, supporting the upper age boundary approach. Log-linear regression models were created to assess risk for severe morbidity with risk ratios and associated 95% confidence intervals as measures of effect. Women aged 10 to 64 years with a diagnosis of HMB (metrorrhagia, menometrorrhagia, and polymenorrhoea) were included in the analysis. The first exposure (RQ1) evaluated was self-reported demographic variables: age (<19, 20-29, 30-39, 40-49, 50-59, and >60 years of age), health status (anemia), insurance status (Medicare, Medicaid, private, uninsured, or other), income for zip code (ZIP code income quartile), and patient residence (large central metro, large fringe metro [suburbs], medium and small metro, micropolitan and noncore [rural], plus missing). The second exposure (RQ2) assessed was the presence of health-related factors, including diabetes and hypertension. The severity of presentation was dichotomized as hospital admission or not, and if a subject received a transfusion or not. The third association (RQ3) evaluated was the patient location. The NRD captured NEDS subjects who were subsequently admitted to the hospital.

The primary outcome of this research project is the characterization of risk factors associated with ED presentation for HMB. Increasing HMB severity is theorized to represent poor health-seeking behaviors including limited access to care. The severity of HMB will be estimated via two dimensions, hospital admission and treated and released. Stratification of the study population by hospitalization will allow for the identification of health determinants associated with a gradation of HMB consequences. The most severe category is proposed to represent either the most severe acute circumstance or represent a state of the most prolonged avoidance of health care. Given the collection methods of the

NEDS secondary data set, separating acute versus chronic severity will not be possible. A binary logistic regression model with hospitalization status as the dependent (outcome) variable will be developed. A fully stepwise selection algorithm for both entry and retention in the model will be constructed. HMB severity will be categorized via hospitalization status (yes or no). Demographic severity descriptions will be analyzed. Hospitalization would indicate greater a risk of morbidity. Significant risk factors will be retained in the model. Adjusted risk ratios for HMB severity with 95% confidence intervals (CIs) as measures of effect will be calculated. The model is designed to account for demographic and hospital factors which will be derived from fitting the log-linear regression model.

Within the overall study population and by severity index description of the demographic and hospital characteristics by NEDS categories will be presented. The hospital characteristics in NEDS include the number of beds (small, medium, or large), geographical location, the academic status captured based on teaching activity (urban teaching, urban nonteaching, and rural), and regional location (Northeast, Midwest, South, or West). Additional demographic categories including insurance status (Medicaid, private, Medicare, other, uninsured), and ZIP code income quartile will be described. Comparisons of severity indexes will be evaluated using the Chi^2 test. Population weights can be applied to data in the NEDS dataset to create national estimates. These weights will be applied in this research. All analyses will be performed with SPSS (v 24).

Data Analysis

Using ICD-10-CM/PCS codes N91, N92, and N93 for metrorrhagia, menometrorrhagia, and polymenorrhoea respectively case records from the 2016 HCUP NEDS and NRD databases will be extracted. Variables to be measured in this study include; age, anemia status, diabetes status, hypertension, insurance status, income, residence location, (table 5). Data will be extracted and loaded from the HCUP source, pre-coded for analysis by SPSS version 24 for analysis. Data will be checked for missing variables and for entry errors. Errors such as coding for male gender and clinical parameters that would be incompatible with life will be performed.

Descriptive statistics will be calculated to characterize the central tendency and dispersion in the data. Odds ratios will be calculated to ascertain the association between HMB that only presents at the ED versus patients who are admitted to the hospital. Factor analysis is will be performed to identify latent variables or factors. Additionally, propensity-matching scores will be calculated to control for comorbidities.

Data Analysis for Each Objective

1. To quantify the differences between HMB patient demographics (age, health status, insurance status) in those who are only treated in the emergency department versus those who are admitted to hospital admission, logistic regression will be used. The odds ratio will be estimated with the 95% confidence interval used to determine statistical significance. Descriptive summary statistics will be described as central tendency and dispersion between both populations.

2. To ascertain the association between health factors (comorbidities such as diabetes and hypertension) admission for menorrhagia, and emergency department presentation outcome (hospitalization admission, Y/N) for heavy menstrual bleeding logistic regression, and discriminant functions analysis was used. These methods will be used to identify potential risk factors contributing to the most severe health situation, admission to the hospital-based on emergency department by presentation of HMB symptoms.
3. To ascertain the association between location (spatial), and economic status logistic regression and discriminant functions was generated to determine variables of importance.

Population

The study population was derived from patient records captured in the HCUP databases, NEDS 2016, the Nationwide Emergency Department Sample, and NRD, the Nationwide Readmissions Database. This data is collected by the Agency for Healthcare Research and Quality. Individual anonymized records will be utilized in this project. Women with a diagnosis of excessive menstruation (ICD-10-CM/PCS codes N92 and N93 for metrorrhagia, menometrorrhagia, and polymenorrhoea respectively) between the ages of 10 and 64 will be included in the study population.

Both NEDS and NRD data are obtained from hospital billing information and include both inpatient and outpatient care. Insured and uninsured patients are captured in addition to Medicare and Medicaid covered individuals. The contributing hospitals are classified as non-federal community hospitals. Approximately 88% of US hospitals are considered non-federal. Those included hospitals are; general multi-specialty community, obstetrics and gynecology, ear nose, and throat (ENT), orthopedic, pediatric, public, and academic medical centers. Excluded entities are 12% of the hospital population. These excluded hospitals are; long-term care facilities, psychiatric institutions, alcoholism/chemical dependency hospitals, rehabilitation, hospital units of other institutions, such as prisons, and Federal hospitals (Veteran's Administration, Department of Defense, Indian Health Service) (HCUPnet, 2018). Additionally, Federal, long-term care, psychiatric, and tuberculosis hospitals are excluded as HCUP data sources. The likelihood of HMB presentation at the excluded entities is assumed to be relatively low.

The design of the NEDS database is to produce both national and regional estimates about emergency department (ED) visits. Information collected and available for analysis includes geographic characteristics (Metro area), hospital characteristics, patient characteristics, and the ICD code for the visit. NEDS is constructed from the HCUP State Emergency Department Databases (SEDD) and the State Inpatient Databases (SID). The SEDD capture discharge information on ED visits that do not result in an admission (i.e., treat-and-release visits and transfers to another hospital). The SID contains information on patients initially seen in the emergency room and then admitted to the same hospital. The NEDS data files are by calendar year.

There are 37 contributing organizations to the 2016 NEDS: AR, AZ, CA, CT, DC, FL, GA, HI, IA, IL, IN, KS, KY, MA, MD, ME, MN, MO, MS, MT, NC, ND, NE, NJ, NV, NY, OH, OR, RI, SC, SD, TN, TX, UT, VT, WI, and WY. These States are geographically distributed and account for 68.7 percent of the total U.S. resident population and 78.2 percent of all U.S. ED visits. Unweighted, the NEDS contains data from 33 million ED visits in 2016. Weighted, the 2016 NEDS describe 145 million ED visits. An important feature of the NEDS database is its large sample size and its representation of the community population. These features allow for analysis across hospital types and the study of specific events such as HMB.

When a patient is admitted into the hospital from the ED, the Nationwide Readmissions Database (NRD) collects this information. These subjects are anticipated to have either a severe bleeding event in need of further attention or present with comorbidities that are exacerbated by the initial bleeding event. This too is a database of all-payer hospital inpatient stays capable of generating national estimates of readmissions. Outcomes collected include national readmission rates, reasons for returning to the hospital for care, and the hospital costs for discharges with and without readmissions. The NRD is drawn from HCUP State Inpatient Databases (SID) containing verified patient linkage numbers that can be used to track a person across hospitals within a State while adhering to strict privacy guidelines. Unweighted, the NRD contains data from approximately 17 million discharges each year. Weighted, it estimates roughly 36 million discharges in the United States.

Twenty-seven States contribute to the 2016 NRD database and subsequent patient population: Alaska, Arkansas, California, Florida, Georgia, Hawaii, Iowa, Louisiana, Maryland, Massachusetts, Mississippi, Missouri, Nebraska, New Mexico, Nevada, New York, Oregon, Pennsylvania, South Carolina, South Dakota, Tennessee, Utah, Virginia, Vermont, Washington, Wisconsin, and Wyoming. These States are geographically dispersed and account for 57.8 percent of the total U.S. resident population and 56.6 percent of all U.S. hospitalizations. This does not completely overlap with NEDS and thus means that weighting estimates applied to estimate national event rates will be potentially more prone to error.

Sampling and Sampling Procedures

The 2016 NEDS and NRD datasets will be utilized for this research. Sampling will be achieved by extraction of cases based on the ICD-10-CM/PCS for HMB. This large anonymous database is suitable to answer the research questions and test the hypothesis that HMB in the community may not be equitably distributed within races and socioeconomic strata. This is the largest publicly available database in the United States.

The sampling frame will include women of reproductive age with the diagnosis of HMB. Women below the age of 10 and above 65 will be excluded on the basis that excessive uterine bleeding will be due to causes other than those associated with reproductive functioning. Extracted health records will be checked for completeness of the seven predictor variables. A quality check for obvious misclassifications of each record will manually be performed. Scenarios of record exclusion include gender categorized as male and any predictor variable that falls outside of expected normal ranges.

Multiple years of data are available to strengthen the external validity of the 2016 findings if required. The sample population with be extracted based onICD-10 codes along with the matching patient records. This research method is appropriate to identify characteristics of at-risk populations within the community (Hilton et al., 2018). Studying comorbidities and their contribution to risk may further contribute to the understanding of variations in HMB.

Power Analysis

Power calculations were performed using G*power software version 3.1 9.2. The model selected was the z test, logistic regression, fixed model, alpha = 0.05, two-tail. Logistic regression analysis will be used to address these public health research questions. The logistic regression approach to collected predictor variables may allow for the development of prognostic models for severity and likelihood of being admitted to hospital. The probability of a dichotomous outcome may well be estimated with a logistic regression model. Ranging effect sizes and estimated odds ratios, table 6 summarizes sample size estimates.

Table 4

Summary of Power Estimates Based on Different Odds Ratios

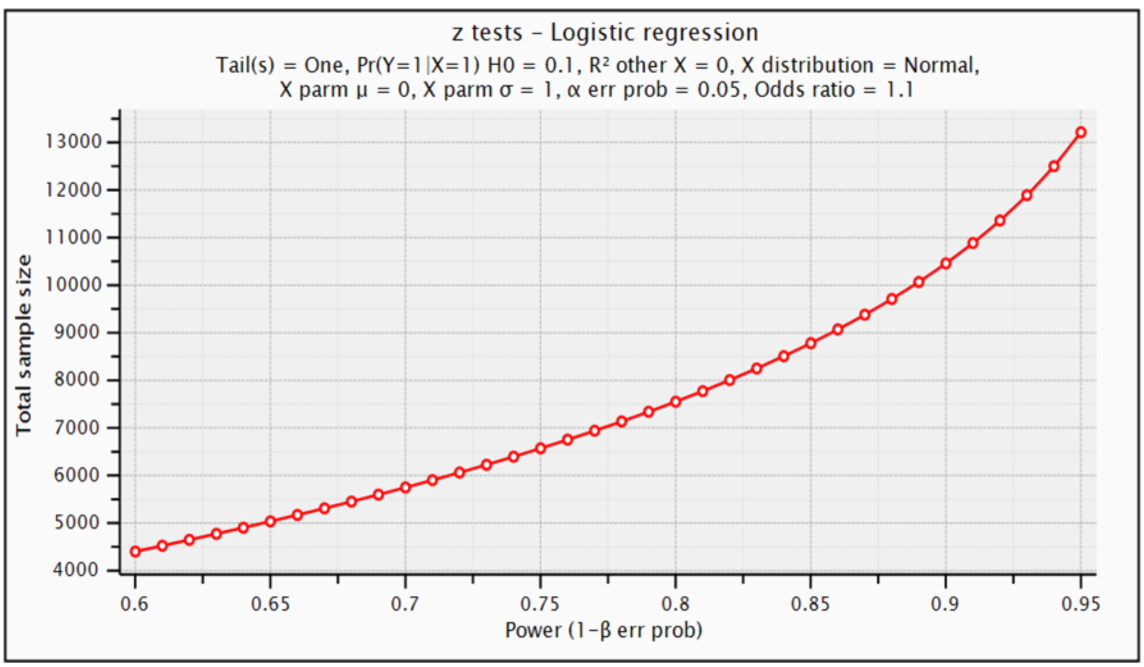
Odds ratio	Effect size	Power	*N*
1.30	0.20	95%	988
1.30	0.10	95%	1727
1.50	0.20	95%	417
1.50	0.10	95%	713
1.50	0.20	80%	242
1.15	0.10	95%	3508
1.10	0.10	80%	7553
1.10	0.10	95%	13216

Gyamfi-Bannerman et al. (2018) explored a similar women’s health endpoint using the HCUP database. The power calculations estimate a minimal sample size N of

13,216 using a conservative estimate of the odds ratio of 1.10 with a minimal effect size of 0.10. With larger odds ratios, the required N substantially decreases. A check of the potential sample size using the HCUP fast stat data analysis tool (accessed November 25, 2018) for the year 2014 recorded 62,589 ED visits for diagnoses ICD-9-CM Codes (ICD9), Principal Diagnosis: 626.2 Excessive Menstruation, and 626.3 Pubertal Menorrhagia. There were 5,088 hospital admissions associated with the ED visits which translates to an admission rate of 8.1%. Based on the power calculations and the conservative effect size, the 2016 data source should be sufficient to explore the research questions.

Figure 3

Power Versus Total Sample Size Estimations for Minimal Effect Size, Odds Ratio 1.10



Data Analysis Plan

Multiple logistic regression analysis will be the primary statistical method utilized to address the research questions. Logistic regression will be employed to ascertain the relative importance of predictor variables in explaining HMB presentation in the ED. Predictor variables to be collected include: age, anemia, diabetes, hypertension, insurance status, income, and patient location. The dependent variable, HBM will be dichotomized to either ED or ED/Hospital admission.

Dataset Description

The Nationwide Emergency Department Sample or NEDS is a database of emergency department visits. The target universe is all emergency department visits from hospital-based emergency department units in the community, non-rehabilitation hospitals in the United States (HCUP.net 2018). The sampling frame is all emergency department visits from hospital-based emergency department units in the community, non-rehabilitation hospitals in the participating HCUP Partner States. NEDS is stratified by US Region, urban or rural location, teaching status, ownership, and trauma-level hospital with a sampling unit of hospital emergency department-level individual HMB cases.

The NRD is a national database of hospital inpatient stays derived from individual state inpatient databases. Patient verified linkage numbers are available to track a patient across hospital stays while adhering to strict privacy guidelines (HCUP 2018). The NRD is designed to enable analyses of national readmission rates. The NRD will permit estimation of national rates of readmission for patient insurance types including the uninsured. Exploration of reasons for returning to the hospital for care and the hospital costs for discharges with and without readmissions are possible.

The NEDS database approximates a 20% sample of hospital-based emergency departments in the U.S. The NEDS sample contains over 950 hospital-based emergency departments. From each selected emergency department, all visits are included. An estimated minimum of 25 million unweighted observations each data year are captured. The NEDS is designed to be nationally representative of emergency-department care since the sampling frame is not designed with the state as a stratification variable. This would support the premise that NEDS will provide population estimates of HMB burden and allow for risk estimation.

Secondary Data From Patient-Reported Events

Using case definition in secondary data for HMB based on The International Statistical Classification of Diseases and Health-Related Problems, ICD-9-CM and ICD-10-CM/PCS codes will rely primarily on patient reported classification of an HMB event. Subjective and self-reporting of blood loss may be considered to be a poor indicator of actual menstrual loss. Reports of the quantity of blood loss women experience each month is difficult to categorize, and precise reporting of blood loss is also problematic (Moon et al., 2017). However, the evidence does indicate a positive correlation with objectively measured blood loss (Quinn, & Higham, 2016). A caveat is that the positive predictive value is low. The validity and strength of patient or self-reported events are gaining interest and credibility (O’Mahony et al., 2016). While individual perceptions may be prone to high degrees of variability, patient-reported outcomes (PRO) data are useful when large sample sets are available to represent community health (Begg et al., 2013). PRO data may contribute to a more complete and deeper understanding of the true population burden and provide insights into the impact of living with a disease (O’Mahony et al., 2016). These studies support the use of self-selected secondary data events as a basis for research. From a social change perspective, utilizing the patient-reported event as being meaningful as well as being a useful indicator of true HMB will allow for risk characterization.

Characterizing risk factors that contribute to HMB will require consideration of both modifiable and non-modifiable factors that are theorized to contribute. Risk variation depends on the population from which the study sample was obtained (Begg, et al., 2013). The cases reported in the database represent individual events. These cases are defined as individuals who have experienced and sought treatment at an ED thus representing the sentinel event. These cases will be included in the analysis. An important consideration is that as in self-controlled case series studies, all time-invariant confounders that act multiplicatively on the baseline incidence are automatically controlled (Whitaker, et al., 2018).

Research Methods

The research method considered is quantitative and retrospective in design. Secondary data analysis will be performed. Interrogation of the Healthcare Cost and Utilization Project — HCUP a Federal-state-industry partnership in health data sponsored by the Agency for Healthcare Research and Quality will be performed. The Nationwide Emergency Department Sample (NEDS) tracks information about emergency department

(ED) visits across the country. Information includes geographic characteristics, hospital characteristics, patient characteristics, and the nature of visits (e.g., common reasons for ED visits, acute and chronic conditions, and injuries). The NEDS was constructed using the HCUP State Emergency Department Databases (SEDD) and the State Inpatient Databases (SID). The SEDD capture discharge information on ED visits that do not result in an admission (i.e., treat-and-release visits and transfers to another hospital). The SID contains information on patients initially seen in the emergency room and then admitted to the same hospital. The NEDS consists of nearly 30 million records, representing over 130 million ED visits. One of the unique features of the NEDS is its large sample size, which allows for analysis across hospital types and the study of relatively uncommon disorders and procedures. The NEDS database will be appropriate to address research questions one, two, and three.

To ascertain the severity of HMB events, admission to the hospital from the ED is proposed to be an appropriate surrogate. The NEDS data indicates admission from the ED. The HCUP nationwide readmissions database (NRD) is derived from the State Inpatient Databases (SID). The NRD is designed to allow research related analyses of readmissions by the same individual. This data is expected to provide evidence for answering research question three. An important limitation of using NRD is that this database cannot be combined across data years to create multi-year analyses. The patient linkage numbers do not track the same person across the years. Also, the hospital identifiers do not track the same hospital across the years. For analysis purposes, each year of the NRD must be considered as a separate sample.

Analytical Approach

Binary (or binomial) logistic regression will be used to address the three primary research questions. Logistic regression is an appropriate method to predict the categorical dependent variable (hospital admission) based on the seven continuous and/or categorical independent or predictor variables. All analyses will be performed using IBM SPSS v25. Data will be provided from the Agency for Health Quality Research via zip files. The data is available in SPSS file format and requires submission of a statement of research as well as completion of health privacy training.

The proposed research will analyze the 2016 (most recent complete dataset) Nationwide Emergency Department Sample (NEDS) for emergency department visits using the ICD-10-CM/PCS diagnostic codes for the most likely diagnostic codes for heavy menstrual bleeding (Elixhauser et al., 2017). The case definition will be based on The International Statistical Classification of Diseases and Health-Related Problems. The ICD-10-CM/PCS uses the terms metrorrhagia, menometrorrhagia, and polymenorrhoea (N91, N92, & N93 respectively) for HMB symptoms (Bahamondes, & Ali, 2015).

Data Modeling

Binary (or binomial) logistic regression is a form of regression that is used when the dependent is a dichotomy and the independents are of any type. Multinomial logistic regression exists to handle the case of dependents with more classes than two, though it is sometimes used for binary dependents. Logistic regression can be used to predict a categorical dependent variable based on continuous and/or categorical independents; to determine the effect size of the independent variables on the dependent; to rank the relative importance of independents; to assess interaction effects; and to understand the impact of covariate control variables (Wang et al., 2018). The impact of predictor variables is usually explained in terms of odds ratios. Logistic regression applies maximum likelihood estimation after transforming the dependent into a logit variable. A logit is the natural log of the odds of the dependent equaling a certain value or not (usually 1 in binary logistic models, the highest value in multinomial models). In this way, logistic regression estimates the odds of a certain event (value) occurring, a central aim to estimate associated risk factors with HMB.

Epidemiologic methods, such as logistic regression, typically analyze data at the individual -level. The variation observed in these approaches may be due to several sources. Individual characteristics (compositional effects), group characteristics (contextual effects), or the effects of omitted group-level variables on individual-level outcomes should be anticipated (Bardenheier, et al., 2005). Logistic regression permits the simultaneous examination of how individual-level and group-level variables relate to individual-level outcomes, thus allowing for contextual effects that likely impact the quality of health care. However, it does not allow the examination of both between- and within-group variability, and how group-level and individual-level variability relate (Begg, & Zabor, 2012). Traditional logistic regression (which, in multilevel analysis terms, is one-level) requires the assumptions: (a) independence of observations conditional on the independent variables and 2) uncorrelated residual errors. These assumptions are not always met when analyzing nested data (e.g., residents clustered in single hospitals). The multilevel analysis will be considered when variability between groups on individual-level outcomes exists is being considered. Since the precise estimation of blood loss is unlikely, HMB as a category is expected to be a very heterogeneous event. Etiologic heterogeneity will make risk estimation potentially more challenging. Having access to a diverse and large sample set may improve the signal to noise ratio and reduce the risk of false discovery.

Factor Analysis

Additional analysis is planned involving factor analysis. Factor analysis is appropriate for examining a dataset with the outcome of identifying latent variables or factors (Pan et al., 2015). Complex causes of events such as heavy menstrual bleeding necessitate examining multiple variables to accurately describe the observed data (Sankoh et al., 2014). An analytic strategy to explore and identify latent variables or factors will be useful. Methods such as factor analysis are appropriate to identify variables that contribute to HMB and describe how each factor's effect may be interpreted (Dmitrienko, & D'Agostino, 2018). If disproportional influences of a specific factor(s) are identified, they may establish potential targets for public health and social change programs. Both exploratory and confirmatory approaches will be considered.

Propensity Scores

Using secondary data limits the feasibility of examining causality. The objective of this research project is non-causal aiming to compare a dichotomous outcome among an HMB population with different characteristics including health status and location. Irrespective of whether the purpose of the research is causal or not, making comparisons between groups can be biased when the groups are not balanced. An important concern occurs when there are substantially different distributions of relevant covariates (Li et al., 2018). The use of propensity scores may be a more effective method than weighting strategies to ensure covariate balance. Propensity scores will be determined for research question two; what is the association between health factors (comorbidities such as diabetes and hypertension) admission for menorrhagia, and emergency department presentation for heavy menstrual bleeding?

Parametric adjustment by regression is often influenced by model misspecification when groups differ greatly in observed characteristics (Robins et al., 2000). A frequently used nonparametric balancing strategy is weighting. Weights may be applied to a sample of units in each treatment group to match the covariate distribution of a target population (Li, & Green, 2013). Weighting approaches can then allow a comparison between the weighted outcomes. The propensity score (PS) will be an important statistical approach for controlling confounding in this observational data set.

Individuals who are admitted to the hospital from the ED are theorized to represent a population who’s HMB represents a high health risk. Important comorbidities or serious consequences due to delayed health-seeking behavior such as profound anemia are expected to be an important reason for admission. This admission or subsequent intervention (transfusion and/or hospital admission) would suggest a concern for immediate well-being. Exploring the influence of factors that contribute to hospital admission will further provide guidance to public health strategies. In an observational study, the factor groups are most likely are not directly comparable. Statistical adjustment for confounders must be considered to minimize bias in outcome estimates.

Rubin (2011) demonstrated that potential outcomes may be formulated to estimate causal effects. This method of determining an average treatment effect (ATE) involved pre-exposure and a binary outcome (Y) – hospitalized or not hospitalized. The binary exposure (factor) denoted as A and the pre-exposure vector of potential confounders W are modeled. Each individual has two potential outcomes: the outcome observed had they had the factor or exposure (A = 1), denoted Y(1), and the outcome had they not been unexposed, Y(0) (Luque-Fernandez et al., 2018). Only one outcome is possible for each individual who presents at the ED. By definition Y(1) is observed for women in the factor (exposure) group and Y(0) only for those not having the factor (unexposed) group. Two estimates are of interest; the average treatment effect (ATE) which in this research will represent an estimate of the influence of important factors. The ATE is defined as $E[Y(1) - Y(0)]$ and the marginal odds ratio (MOR) is defined as $E[Y(1)] \times \{1 - E[Y(0)]\}/\{E(1 - E[Y(1)]) \times E[Y(0)]\}$ (Luque-Fernandez et al., 2018). Several statistical concerns exist.

A key assumption may be violated trying to estimate ATE. Identification of ATE by logistic regression models where the factor is included as a covariate in the analysis assumes that the effect measure of the factor of interest is constant across the levels of confounders included in the model (Luque-Fernandez et al., 2018). In the secondary observational data set several assumptions cannot be validated. Greenland and Robins (1986) introduced the G-formula to address the violation of the assumption’s constant effect. They showed that under the untestable causal assumption required for ATE estimation an alternative model may be used. They demonstrated that when conditional exchangeability, positivity, consistency, and noninterference assumptions cannot be met, a reliable estimate of the ATE can be obtained by using the generalization of standardization or G-formula. This approach considers the confounder distribution:

$$ATE = \Sigma_W [\ \Sigma_y P(Y= y \mid A = 1, W = w) - \Sigma y\ P(Y - y \mid A = 0, W = w)\ ]\ P(W = w)$$

An attractive attribute of using the G-computation is that it is based on the estimation of the components in the G-formula. This allows for a factor effect to exhibit variation across levels of the confounders. A requirement is parametric modeling assumptions and bootstrapping for the estimation of the standard error (Rubin, 2011). An important limitation is that the G-computation is sensitive to model misspecification. The estimation of confidence intervals (CIs) is also complex. These limitations make G-formula utilization limited.

An alternative approach is to consider the propensity score to estimate the factor contributing to the outcome (Luque-Fernandez, Schomaker, Rachet, & Schnitzer, 2018). Propensity score methods, introduced by Rosenbaum and Rubin (1983), estimate the treatment mechanism. In our setting, where treatment is assigned at a single time point, the propensity score is defined as the probability of being treated given the observed confounders W, denoted P(A = 1|W). The propensity score is used to statistically balance exposure groups in their pre-exposure covariates to estimate the ATE. This may be done via matching, weighting, or stratification. When weighting by the inverse of the propensity score, extreme values of the propensity score can lead to large weights, resulting in unstable ATE estimates with high variance (in particular, ATE estimates can fall outside the constraints of the statistical model). Furthermore, when analyzing observational data with a large number of variables and potentially complex associations among them, model misspecification is of particular concern in this case as well. Hence, correct model specification is crucial to obtain unbiased estimates of the true ATE. (Bühlmannet al., 2016).

Threats to Validity

An important threat to validity is to use data for research purposes for which they are not specifically generated (Kuriyama et al., 2017). Secondary data collected from external sources will be dependent on the rigor of the collection methods. A central element of the validity of these research findings will be the accuracy of the disease status. Electronic records in HCUP which rely on a categorical code such as the ICD-10-CM/PCS or ICD-9CM have been found to be reliable. Studies that have compared diagnoses and procedures reported in administrative data compared with medical records have found acceptable levels of agreement (Casey, Schwartz, Stewart, & Adler, 2016). Hsu et al. (2014) found that the positive predictive value (PPV) for the ICD-9 code 471.x for nasal polyps was 85%. This would support the premise that those with the diagnostic code do indeed have the disease.

Internal Validity

Generation of reliable risk estimates via the HCUP secondary data will require addressing bias, confounding, and random error as alternative explanations (Casey et al., 2016). While large sizes reduce the bias due to random error, bias due to measurement error is independent of sample size (Mooney et al., 2015). Estimation of measures of association will be the outcome of the proposed research. To ensure minimal threats to internal validity several sources was assessed. Uses of hospital records have limitations.

Sources of bias to eliminate or minimize from these records can include the following:

1. Selection bias: Self-selection is a concern as the recorded cases will reflect women who are theorized by the Theory of Reasoned Action (TRA) to be motivated to seek attention driven by a perception of a health crisis. A key premise of this theory is that HMB symptoms and combined health-related effects are substantial enough to seek urgent care at the ED. This cohort would represent the target population who by definition are exhibiting active symptoms, health consequences, and are at risk for a further decline in health status.
2. Data collection and misclassification bias: consistency in measurement. Will the outcomes be measured or recorded differently by different health care providers. Based on the ICD classification system and the broad definition of HMB, using diagnostic codes ICD-10-CM/PCS terms for metrorrhagia, menometrorrhagia, and polymenorrhoea (N91, N92, N93), and ICD-9-CM codes for metrorhagia (626.6), uterine leiomyoma (218), excessive or frequent menstruation (626.2) and premenopausal menorrhagia (627.0) should be sufficient to generate a study population with a consistent definition of HMB.
3. Attrition bias: Subjects will remain to contribute as long as they continue in the health care system and seek care (Casey et al., 2016). As each ED

presentation is an incident event of interest, continuous enrollment in a health care system should minimize this bias. However, if access to the system is interrupted, then underestimation of the magnitude of the population health problem may occur. The motivation to seek care in the ED is theorized to be driven by high degrees of severity which is expected to reduce attrition effects in individuals with access and also strengthen the likelihood of accurate disease coding.

4. Nonparticipation bias: Another element of a systematic error related to participation in the health care system. Nonparticipation is expected to result in underestimation of the overall population problem, and potentially skew the study population towards individuals with higher income, educational attainment, and access to health care resources. Individuals who choose not to seek care are theorized to have symptoms that may be deemed non-severe or having minimal impact on the quality of life.
5. Recall bias: Likely to be minimal by using patient record data collected at the time of ED presentation.
6. Statistical regression: possible but reduced by large sample size.

I did not explore an association between exposure and HMB. Confounding by extraneous effects such as age and other factors will be stratified and adjusted for. Confounding by indication and severity must be discussed. The presence of symptoms (indication) is the selection criteria for inclusion. The severity of symptoms will represent a stratum that the ICD codes will not be able to categorize. This study will use the criteria of hospital admission as a surrogate for either severe symptoms requiring additional complex management or a compromised health state that requires additional support. In either case, hospital admission from the ED will be classified as a severe health state.

Random error due to inaccurate HMB classification will be assessed by screening the study population data for errors such as a male being coded for HMB. Elimination of records containing men presenting with HMB will be done. Also, women below and above the reproductive age bands of 10 years on the bottom and 65 years on the top will be considered unlikely to have HMB. The HCUP allows for the identification of women who are readmitted for the same indication in the NRD. To account for multiple readmissions, within 30 days, only the first readmission will be included.

Interpretation of the analysis should keep in mind several limitations. First, the data is sourced from administrative records and does not provide information on elements that may influence outcomes such as resources within a hospital, staffing, protocols, and the infrastructure. These inputs may contribute to the interventions utilized and admission decisions. Detailed data on individual patient management are also not available. This research cannot determine the overall health burden associated with HMB presentation.

The second limitation is that the exposure event was identified through hospital record coding. Any misdiagnosis or comorbid conditions being coded as the initial diagnosis could lead to an underestimation of HMB events. Third, estimating the actual disease burden from HMB is a challenge using this data. Factors involved in the classification of the most severe situation; hospital admission and the decision to treat or counter anemia (transfusion) may be driven by factors not available in the health record.

External Validity

The generalizability of the findings will be established once the study population is described and characterized. The primary concern will be how representative the sample is. Subjects who seek attention in the ED are theorized to have severe symptoms prompting health-seeking action. This population may not be representative of individuals who have access to gynecological care and would thus be managed in a physician's office. The HCUP databases do not capture such visits. These HMB visits collected in NEDS and NRD will be limited to those seeking attention in an ED. The study sample will thus represent the more serious or troublesome conditions and not the mild conditions.

Ethical Procedures

An important ethical procedure is an assurance that the risk of unintentional disclosure of personally-identifying information is eliminated (Mooney, & Pejaver, 2018). The HCUP databases are consistent with the definition of limited data sets under the HIPAA Privacy Rule and contain no direct patient identifiers. Data released to AHRQ for the HCUP Databases are subject to the data standards and protections established by the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (P.L. 104-191) and implementing regulations ("the Privacy Rule"). Consequently, HCUP Databases may only be released in "limited data set" form, as that term is defined by the Privacy Rule, 45 C.F.R. § 164.514(e). HCUP data may only be used by the data recipient for research which may include analysis and aggregate statistical reporting. AHRQ classifies HCUP data as protected health information under the HIPAA Privacy Rule, 45 C.F.R. §

160.103. The Walden University IRB approval number for this research is 08-06-19-0414061.

Summary

The 2016 NEDS dataset was used for this research. This large anonymous database is suitable to answer the research questions and test the hypothesis that HMB in the community may not be equitably distributed within geographic location and socioeconomic strata. This is the largest publically available database in the United States. Multiple years of data are available to strengthen the external validity of the 2016 findings. Logistic regression was used to predict a categorical dependent variable based on continuous and/or categorical independents; to determine the effect size of the independent variables on the dependent; to rank the relative importance of independents; to assess interaction effects, and; to understand the impact of covariate control variables.

Characterizing the incidence and risk factors for women who present at the ED with HMB symptoms is not well known. Quantifying risk factors associated with presentation including age, comorbidities such as diabetes, hypertension or, metabolic challenges remains unexplored. Studying comorbidities and their contribution to risk may further contribute to the understanding of risk and variations in HMB.

Chapter 4: Results

Introduction

The consequences of protracted HMB include anemia, chronic fatigue, and decreased psychosocial wellbeing (Kassebaum et al., 2014). EDs are often the first point of medical contact and may function as a health sanctuary for those with limited healthcare access or for those who have ignored bleeding symptoms (Livesey et al., 2016). ED presentation for menorrhagia may indicate that an individual has exceeded a tolerance threshold (Sriprasert et al., 2017). Those without access to gynecological services may be at increased risk for secondary health issues. Characterizing the incidence and comorbidities for women who present at the ED with HMB symptoms is not well known. Quantifying risk factors associated with presentation, including age, comorbidities such as diabetes, hypertension, or health challenges, remain unexplored. Additionally, understanding hospital admission rates could further help quantify the severity of inadequate care suspected to be the result of limited access to gynecological attention (Demers et al., 2006).

Methodology

The methodology captured ED HMB presentations via the NEDS database and hospital admission events via the NRD. The ICD-10-CM/ PCS diagnostic codes for metrorrhagia, menometrorrhagia, and polymenorrhoea (N92 & N93) respectively were used to create the study population. Because the individual data and source hospitals are both de-identified, the university institutional review board’s privacy and patient protection rules were satisfied.

Women of reproductive age with the diagnosis of HMB were included in the study sample. Women under the age of 10 and above 60 were excluded on the basis that excessive uterine bleeding would be due to causes other than those associated with reproductive functioning. Log-linear regression models was created to assess risk for severe morbidity with risk ratios and associated 95% CIs as measures of effect. Women aged 10 to 60 years with a diagnosis of HMB (metrorrhagia, menometrorrhagia, and polymenorrhoea) were included in the analysis. The first exposure (RQ1) evaluated self-reported demographic variables and age (<19, 20-29, 30-39, 40-49, 50-60 years of age); ethnicity was not analyzed as many states do not identify race in their reporting data sets. Additionally, health status (anemia), insurance status (Medicare, Medicaid, private, uninsured, or other), income for zip code (ZIP code income quartile), and patient residence (large central metro, large fringe metro [suburbs], medium and small metro, micropolitan and noncore [rural]) data was analyzed. The second exposure (RQ2) assessed the presence of health-related factors, including diabetes, depression, headache, nausea, low back backache, and hypertension. The severity of presentation was dichotomized as admission to a hospital or not, and if a subject received a transfusion or not. The third association (RQ3) evaluated was the location. I assumed that access to specialized care and comprehensive resources was more likely available in larger metropolitan locations versus micropolitan and rural communities. The NRD captured NEDS subjects who were subsequently admitted to hospital.

The primary outcome of this research project is the characterization of risk factors associated with ED presentation for HMB. Increasing HMB severity is theorized to be associated with poor health-seeking behaviors, including living conditions of limited access to primary care via location or insurance status. The severity of HMB was estimated via two dimensions, hospital admission and those diagnosed with HMB. Subjects hospitalized were deemed to have the greatest health burden. Those women with HMB who are hospitalized are proposed to either represent the most severe acute circumstance or represent a state of the most prolonged avoidance of health care. Given the collection methods of the NEDS secondary data set, assessing the associated quality of life was not possible. I developed a binary logistic regression model with hospitalization (yes or no) as the dependent (outcome) variable. A fully stepwise selection algorithm for both entry and retention in the model was constructed. HMB severity was categorized via hospitalization status. I also describe demographic descriptions. Significant risk factors were retained in the model. I calculated adjusted risk ratios for HMB severity with 95% CIs as measures of effect. The model was designed to account for demographic and hospital factors, which were derived from fitting the log-linear regression model.

In addition, I describe demographic categories including insurance status (Medicaid, private, Medicare, other, uninsured) and ZIP code income quartile. Comparisons of severity indexes were evaluated using the Chi^2 test. Population weights can be applied to data in the NEDS dataset to create national estimates. These weights were applied in this research. All analyses were performed with SPSS (v 25).

Results

The HMB presentation was captured from the ED presentations via the NEDS database. The 37 contributing states are distributed evenly by geographical regions. They accounted for 68.7% of the total U.S. resident population and 78.2% of all U.S. ED visits. The International Classification of Diseases, tenth revision, Clinical Modification (ICD-10-CM/ PCS diagnostic codes for metrorrhagia, menometrorrhagia, and polymenorrhoea (N92, N93) respectively were used to create the study population, see Table 7. These codes captured both HMB and abnormal uterine bleeding. Both terms are frequently used for bleeding that is characterized as either heavy and/or irregular (Rosen et al., 2020).

Table 5

Heavy Menstrual Bleeding ICD-10-CM Codes Used for Cohort Extraction

ICD-10-CM code	Description
N92.0	Excessive frequent menstruation with the regular cycle
N92.1	Excessive and frequent menstruation with an irregular cycle
N92.2	Excessive menstruation at puberty
N92.3	Ovulation bleeding
N92.4	Excessive bleeding in the premenopausal period
N92.5	Other specific irregular menstruation
N92.6	Irregular menstruation
N93.0	Other abnormal uterine and vaginal bleeding
N93.8	Other specified abnormal uterine and vaginal bleeding
N93.9	Abnormal uterine and vaginal bleeding unspecified

To create the study cohort, I used the primary core diagnosis (I10_Dx1). The NEDS 2016 core data file contained 32,677,936 patient records. Using the SPSS command “case select,” 111,555 cases were extracted using the ICD-10-CM identification codes listed in Table 7. This data set filtered for age (SPSS command

“AGE >= 10 AND AGE <= 60”) and checked for coding errors, such as males in the data set. Table 8 describes the summary age demographics of the 10 HMB ICD-10 codes used. Three codes, N92.0, N93.8, and N93.9, represented 89.96% of the selected cases. I performed analyses using the entire NEDS HMB cohort.

Table 6

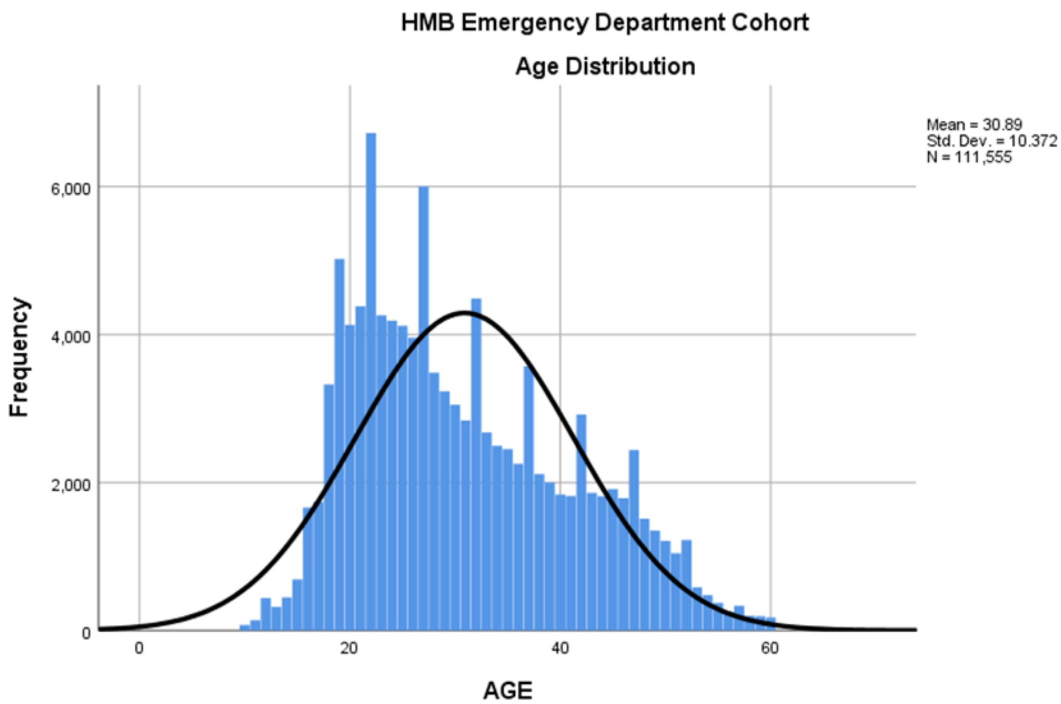
Demographic Distribution of ED Presenting Women by HMB ICD-10-CM Code

ICD-10-CM HMB Code	*N*	Age		
		Mean	Median	Mode
92.0	11,485	31.20	30	22
92.1	5,406	30.48	29	22
92.2	63	13.92	12	12
92.3	27	25.59	24	22
92.4	597	44.09	47	50
92.5	444	27.69	25	22
92.6	4,267	25.69	24	22
93.0	346	27.93	26	18
93.8	40,771	31.34	29	22
93.9	48,102	30.84	28	22
Total	111,555			

The mean age of the entire HMB ED cohort was 30.89 years, the median was 29.00, and the standard deviation was 10.37 years, see Figure 4. The interquartile range was 16 years (IQR = 21 – 37). The mode was 22 years of age (*N* = 6,197). The distribution skewness was +0.517, indicating that most of the HMB cases were at the younger end of the age spectrum. Kurtosis was -0.517, indicating that the curve is flat.

Figure 4

Age Distribution of HMB ED Cohort, NEDS Dataset



The presentation was evenly distributed throughout the calendar year, see Table 9. No seasonal variation was detected among the 99,446 valid cases. The expected admission by month was 8,287 patients. The HMB cohort admission frequency ranged from a low in December of 7,528 presentations (7.57%) to a high in August of 8,819 cases (8.89%), see Table 9. The 95% CI was 282 (95% CI: 8,005 – 8,569). During the week, 74.6% (*N* = 83,268) of cases presented from Monday to Friday. The weekend presentation was lower than expected, 25.4% (*N* = 28,285) of cases. An expected weekend total assuming equal distribution by day would be 31,873 patients. The quarterly distribution of discharges was uniform. Quarter 1 was 24.8%, Quarter 2 was 25.1%, Quarter 3 was 26.2%, and Quarter 4 was 23.8%.

Table 7

Monthly Distribution of HMB ED Presentation

Month	***N***	Frequency (%)
January	8700	8.75
February	7568	7.61
March	8389	8.44
April	8343	8.39
May	8543	8.59
June	8070	8.11
July	8708	8.76
August	8819	8.89
September	8554	8.60
October	8417	8.85
November	7807	7.85
December	7528	7.57

The majority of the NEDS HMB cohort women were treated routinely, referred to as treat and release, N =105,742 (94.8%). The 5,813 women who were not released had outcomes recorded in table 4.4. Of note, the death rate recorded was very low (0.10%). A majority of women, 48.49% decided for reasons unknown to leave the ED against medical advice. A majority of the HMB women had multiple diagnoses at ED presentation, Figure 5.

Figure 5

Number of Diagnoses Associated With Each Patient

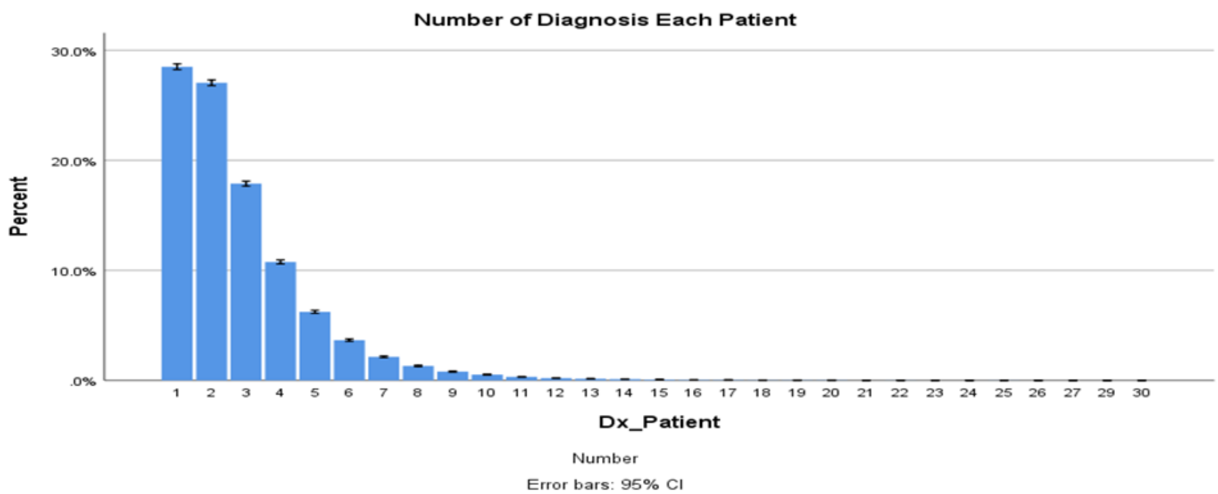


Table 8

Disposition of Women Not Treated and Released From the ED

ED disposition	***N***	Frequency (%)
Transfer: short term hospital	466	8.02
Transfer: another type of facility	207	3.56
Home health care	32	0.55
Against medical advice	2,819	48.49
Admitted as an inpatient to the hospital	2,167	37.28
Died in ED	6	0.10
Not admitted to this hospital, destination unknown	116	2.00
Total	5,813	100.00

Patient location and income are theorized to be important determinants to health status (Diez Roux 2001). The HMB cohort location is described in Table 11. There is an excess of cases from large metropolitan areas (58.17%) versus smaller and rural areas

(41.57%). Large central metropolitan areas contributed significantly ($P < 0.001$) more patient cases ($Chi^2_{Calc} = 49{,}477$).

Table 9

Geographic Distribution of HMB ED Cohort

Location	***N***	Frequency (%)
Large central metropolitan	41,841	37.51
Large fringe metropolitan	23,051	20.66
Medium metropolitan	22,136	19.84
Small metropolitan	10,066	9.02
Micropolitan	8911	7.99
Rural	5264	4.72
Missing	286	0.26
Total	111,555	100.00

Income is also an important determinant of health (Erwin, & Brownson, 2017). Analysis of the median household income quartiles for the HMB patient's ZIP code shows a significant trend towards patients coming from the lowest income strata, Table 12. Comparing $1-42,999 with next income strata $43,000-53,999, the 13.37% difference was significant $P < 0.0001$ (95% CI: 12.69% to 14.05%). The lowest two median household income quartiles represent 65.81% of the patient cohort. This trend would be consistent with the expectation that the emergency department serves a role in providing medical care access to the poorest segment of society.

Table 10

Median Household Income Quartile by Patient ZIP Code

Median household income	***N***	Frequency (%)
$1 – $42,999	44,160	39.59
$43,000 - $53,999	29,246	26.22
$54,000 - $70,999	21,886	19.62
$71,000 or more	14,822	13.29
Missing	1,441	1.29
Total	111,555	100.01

The cost associated with ED presentation is not inconsequential. Total charges exhibit wide variation, Table 13. From the ED cohort total, associated charges for 86.56% of cases where charges was reported is $325,756,680. The charges were heavily skewed to the lower cost range, skewness coefficient = 5.184. The 10th percentile cost is $854; the 90th percentile is $6,629. The mean charge for an HMB patient was $3,373.37, mode $2,150.00.

Table 11

Total Charges Associated With HMB ED Visit, N = 96,567

Mean (St Error)	Median[a]	Mode	Range	Min	Max	Total charges
$3,373 (10.86)	$2,486	$2,150	$127,217	$100	$127,317	$325.8 M

a: calculated from grouped data

Research Question 1

RQ1: What is the association between demographic (age), health status (anemia), insurance status, and ED presentation for HMB?

$H_0$1: There is no statistically significant association between demographic factors (age), health status (anemia) insurance status, and presentation to the emergency room for women of reproductive age in the United States.

*H*a1: There is a statistically significant association between demographic factors (age), health status (anemia) insurance status, and presentation to the emergency room for women of reproductive age in the United States.

Anemia cases were selected using ICD-10/CM code D64.9 with Dx_1 as the secondary diagnosis filter. Analysis of the association between age, anemia, and insurance status is summarized in Table 14. One-way Analysis of Variance (ANOVA) found a significant anemia burden in the 40-49-year age group, $p = 0.012$ (F = 10.51), Figure 6. The mean age of women presenting with anemia is 34.81 years, the mode was 42 and 47 years (227 cases each). Women between 40-49 years had an incidence rate of 7.41% for anemia as comorbidity, double or greater proportionately than the other age groups.

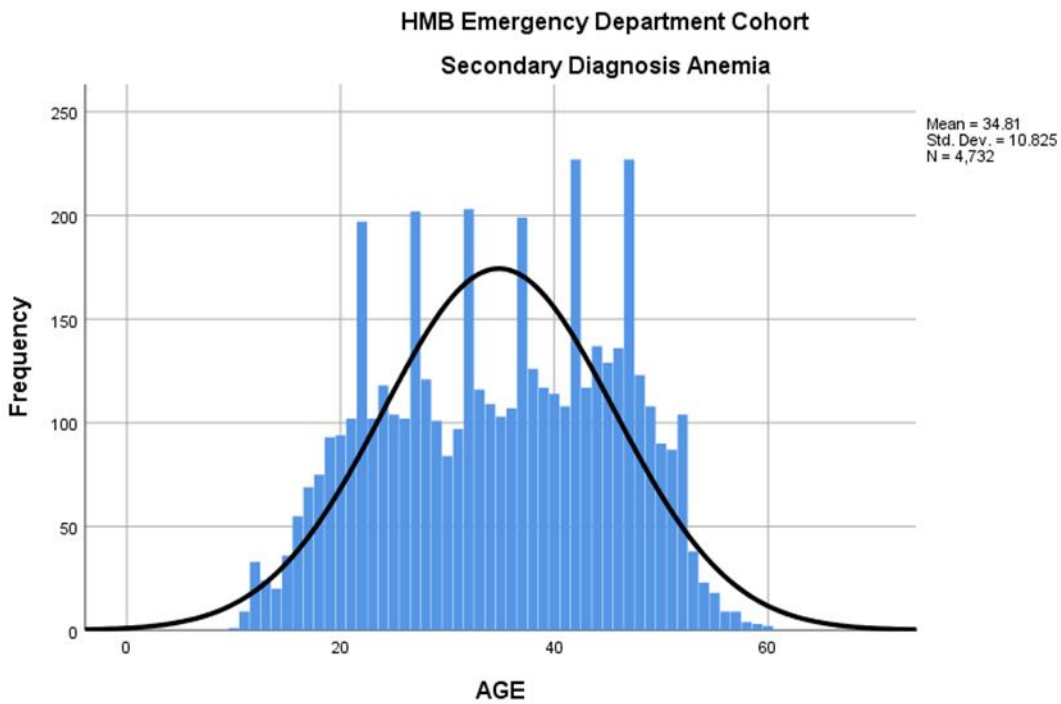
Table 12

Association Between Age, Anemia, and Insurance Status

Age	*N*	Anemia	Insurance status					
		D64.9 (%)	Medicare	Medicaid	Private	Self	No Charge	Other
10 – 19	13,853	415 (3.00)	3	266	106	64	1	15
20 – 29	44,466	1,243 (2.80)	13	501	333	347	11	36
30 – 39	27,929	1,261 (4.52)	44	487	415	248	12	54
40 – 49	19,241	1,426 (7.41)	55	444	581	723	50	185
50 - 60	6,066	387 (6.38)	19	105	186	60	6	11
Total	111,555	4732 (4.24)	134 (0.12)	1803 (1.61)	1621 (1.45)	1442 (1.29)	80 (0.07)	292 (0.26)

Figure 6

Anemia Distribution Among HMB ED Cohort



Insurance status among women with anemia revealed several trends. Of the 4,732 cases Medicaid, private insurance, and self-payment represented 92.67% of the insurance status. Each of these three payment schemes were consistently distributed across all age groups. The chi-square test for independence rejected the null hypothesis that insurance status was the same for all age groups of HMB women with anemia. The calculated λ^2 = 3858 was well above the critical value $\lambda^2_{df = 20, \alpha = 0.05} = 10.85$

Overall health in the women who seek medical care via presentation in EDs is theorized to seek care when health concerns reach a tipping point. Anemia prevalence in the HMB cohort was expected to be greater than the rate found in the general population. The Theory of Reasoned Action may explain differences in the anemia prevalence between the general US population and the HMB cohort. A recent study from the National Health and Nutritional Examination Surveys (NHANES) data may provide context (Le, 2016), Table 15. In the direct age group comparisons, women in the 30-39, 40-49, and 50-50 had significantly higher rates in the HMB cohort versus the NHANES population of the same year. The overall incidence of anemia in the HMB cohort was always greater.

Table 13

HMB Cohort Anemia Frequency Versus NHANES Prevalence

HMB cohort			NHANES cohort		
Age	Anemia prevalence	95% CI	Age	Anemia prevalence	95% CI
10 - 19	3.00	2.71 - 3.30	12 - 14	0.9	0.4 - 1.4
20 - 29	2.80	2.64 – 2.96	15 - 29	2.4	1.8 - 3.0
30 - 39	4.52	4.37 - 4.88	30 - 39	3.2	2.5 - 3.9
40 - 49	7.41	7.03 - 7.81	40 - 49	4.5	3.5 - 5.5
50 -60	6.38	5.76 – 7.05	50 - 59	1.6	1.0 - 2 .1

Comparisons between anemia proportions by age revealed several significant differences, Table 16. Older age groups were generally significantly different. The second oldest cohort (40-49 years) had a significantly greater proportion of women with the comorbidity of anemia versus each age group except versus age 50-60. Women under age 29, in both groups, had significantly less anemia versus the older women. The greater proportion of anemia in older women supports the model that HMB is an increasing health burden with age.

Table 14

Comparison of Anemia Proportion in HMB ED Cohort by Age

Age	10-19 P-value difference (95% CI)	20-29 P-value difference (95% CI)	30-39 P-value difference (95% CI)	40-49 P-value difference (95% CI)	50-60 P-value difference (95% CI)
10-19	-	0.832 0.2% (-1.45 to 2.46)	0.179 1.52% (-0.83 to 3.32)	0.0013 4.41 (1.95 to 6.35)	0.029 3.38% (0.44 to 6.53)
20-29		-	0.0221 1.72% (0.24 to 3.23)	<0.0001 4.61% (2.96 to 6.28)	0.0010 3.58% (1.28 to 6.57)
30-39			-	0.0017 2.89% (1.09 to 4.68)	0.140 1.82% (-0.55 to 4.92)
40-49				-	0.487 1.03% (-2.12 to 3.54)
50-60					-

Research Question 2

RQ2: What is the association between health factors (comorbidities such as diabetes and hypertension), admission for menorrhagia, and ED presentation for HMB?

$H_0$2: There is no association between health factors (comorbidities such as diabetes and hypertension) and presentation to the emergency room for women of reproductive age in the 37 states participating in the Nationwide Emergency Department Sample (NEDS) in the United States.

*H*a2: There is an association between health factors (comorbidities such as diabetes and hypertension) and presentation to the emergency room for women of reproductive age in the 37 states participating in the NEDS in the United States.

Health-related challenges might present in several forms. Heavy menstrual bleeding is often associated with medical comorbidities and downstream health-related problems (Borzutzky, & Jaffray, 2020). These comorbidities may include physical problems such as low back pain, headache, and nausea. Additional wellness indicators such as diabetes, hypertension, and depression might also reflect on the propensity of these women to ignore other important health determinants. Examination of several comorbidities is listed in Table 17.

Table 15

Comorbidity ICD-10-CM Codes

ICD-10-CM code	Description
D64.9	Anemia
I10	Essential primary hypertension
E11.9	Diabetes type II
R51	Headache
R11.0	Nausea
M54.5	Low back pain
F32.9	Depression applicable to generalized unhappiness

The HMB cohort was interrogated for each of the comorbidities. Table 18 summarizes the overall frequencies; Table 19 provides details for each HMB code. The overall admission rate was 2.82%, with 3,149 women being admitted. Physical complaints appear to be relatively minor in this population.

Table 16

Comorbidity Frequency in HBM Cohort

Comorbidity	Number	Frequency
Anemia	4,732	4.24%
Hypertension	3,194	2.86%
Diabetes	841	0.75%
Headache	654	0.59%
Nausea	590	0.52%
Low back pain	500	0.45%
Depression	412	0.37%

Table 17

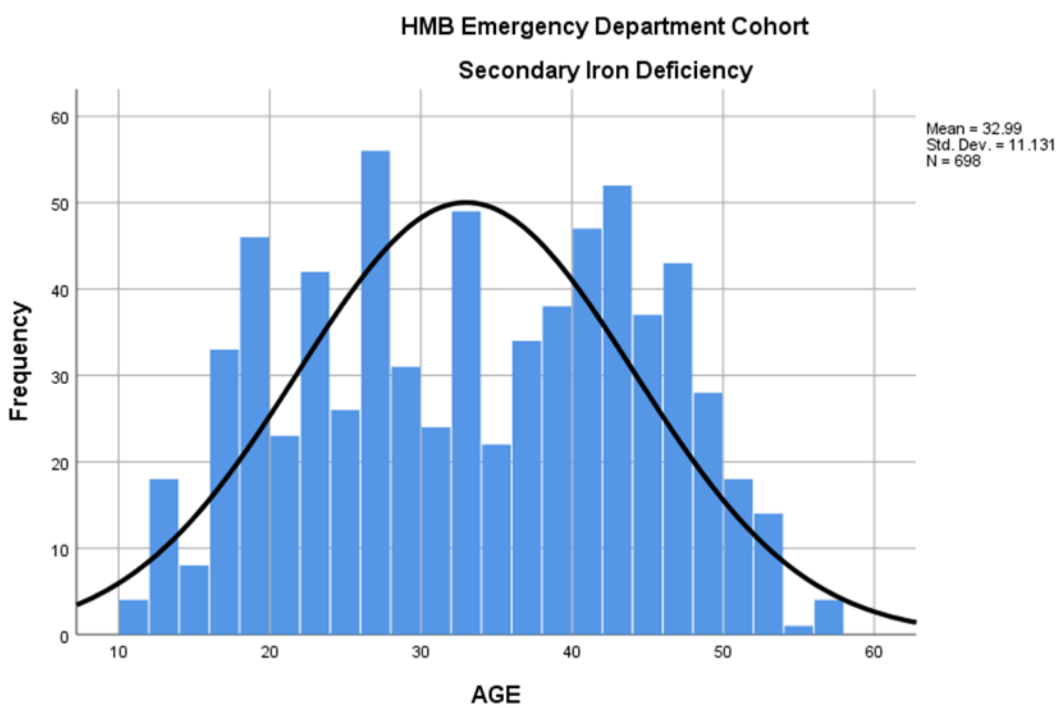
HMB Comorbidities of ED Presenting Women by HMB ICD-10-CM Code

ICD-10 Code	Anemia (%)	Hypertension (%)	Diabetes (%)	Depression (%)	Headache (%)	Nausea (%)	Low back pain (%)	Hospital admission (%)
N92.0	801 (6.96)	304 (2.64	41 (0.36)	38 (0.33)	61 (0.53)	56 (0.49)	41 (0.36)	735 (6.38)
N92.1	292 (5.39)	150 (2.77)	47 (0.87)	20 (0.37)	29 (0.54)	21 (0.39)	17 (0.31)	345 (6.37)
N92.2	3 (4.5)	0	0	0	0	0	0	2 (3.03)
N92.3	0	0	0	0	0	0	1 (3.40)	1 (3.70)
N92.4	35 (5.7)	48 (7.64)	5 (0.80)	3 (0.48)	4 (0.64)	0	1 (0.16)	71 (11.31)
N92.5	11 (2.48)	7 (1.58)	1 (0.23)	1 (0.23)	1 (0.23)	3 (0.68)	2 (0.45)	6 (1.35)
N92.6	57 (1.44)	54 (1.35)	23 (0.57)	15 (0.37)	33 (0.82)	59 (1.47)	23 (0.57)	13 (0.37)
N93.0	2 (0.58)	5 (1.44)	5 (1.44)	0	0	0	2 (0.58)	15 (4.19)
N93.8	2049 (4.99)	1332 (3.24)	366 (0.89)	155 (0.38)	273 (0.66)	216 (0.53)	177 (0.43)	893 (2.12)
N93.9	1482 (3.08)	1294 (2.69)	353 (0.73)	180 (0.37)	244 (0.51)	256 (0.53)	236 (0.49)	1066 (2.22)
Total	4,732 (4.24)	3,194 (2.86)	841 (0.75)	412 (0.37)	654 (0.59)	590 (0.52)	500 (0.45)	3149 (2.82)

History of anemia would suggest chronic blood loss (Sekhar, et al., 2017). Examining the HMB cohort for a secondary diagnosis of iron-deficient anemia, (unspecified) ICD-10-CM D50.9 resulted in 689 women being identified. The mean age is 32.99, years, median 32.86, mode of 42 and range was between 11 and 57 years, Figure 7. This distribution was significantly older (1.97 years) than the HMB cohort, mean age 32.86 versus 30.89 years, $P < 0.001$(95% CI: 1.1929 - 2.7471).

Figure 6

Secondary Iron Deficiency Among HMB ED Cohort



Women with iron deficiency were also more likely to come from the lowest household income strata, 44.29%; between $1 - $42,999. Compared to the overall HMB cohort (39.59), this was numerically greater but not significantly different, $P = 0.128$. The lowest income group was significantly greater in proportion than the next most frequent group ($43,000 – 53,999), 44.29% versus 25.83%, λ^2 = 13.771 p = 0.002 (95% CI: 8.9639% - 27.5334%). The proportion of these women being in poverty was high. Total charges associated with iron deficiency were greater compared to the HMB cohort. The mean charge in the ED was $4,364.97, the median charge $2,957.00. Total charges ranged from a minimum of $271 to a maximum of $35,674.00. Compared to the HMB cohort, the Mean difference of $991 was significantly greater, *P* <0.001 (95% CI: 712.2287 to 1269.7713).

Transfusion Cohort

Women who have lived with a heavy menstrual bleeding burden for years are theorized to be at greater risk for more intensive interventions at the ED. Prolonged excessive bleeding cycles may lead to iron loss, anemia, and the need for interventions (Sekhar et al., 2017). Potential consequences include being admitted to the hospital and being transfused in the ED. Examining the NEDS HMB cohort for transfusions using CPT code 36430 (transfusion, blood, or blood components) identified 339 women who received a transfusion. The mean age was 39.45 years (SD 9.934), Figure 8. Compared to the overall HMB cohort, and other anemia comorbidities, the women who received a blood transfusion in the ED were significantly older, Table 20

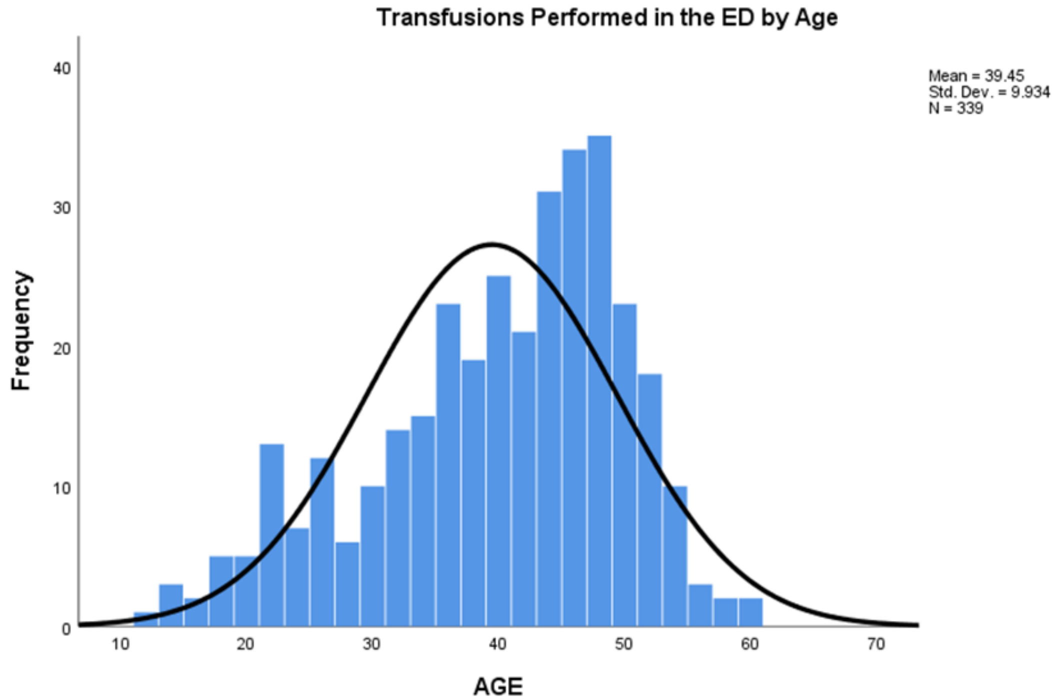
Table 18

Blood Loss Comorbidity Comparisons

Comorbidity	N	Mean (SD)	HMB P-value Difference (95% CI)	Anemia P-value Difference (95% CI)	Secondary Iron Def P-value Difference (95% CI)	Transfusion P-value Difference (95% CI)
HMB Cohort	111,555	30.89 (10.37)	-	<0.001 3.92 (3.62 to 4.22)	<0.001 2.10 (1.33 to 2.87)	<0.001 8.56 (7.45 to 9.67)
Anemia	4,732	34.81 (10.83)		-	< 0.001 -1.82 (-2.68 to -0.96)	<0.001 4.60 (3.46 to 5.82)
Secondary Iron Deficiency	698	32.99 (11.13)			-	<0.001 6.46 (5.08 to 7.83)
Transfusion	339	39.45 (9.34)				-

Figure 7

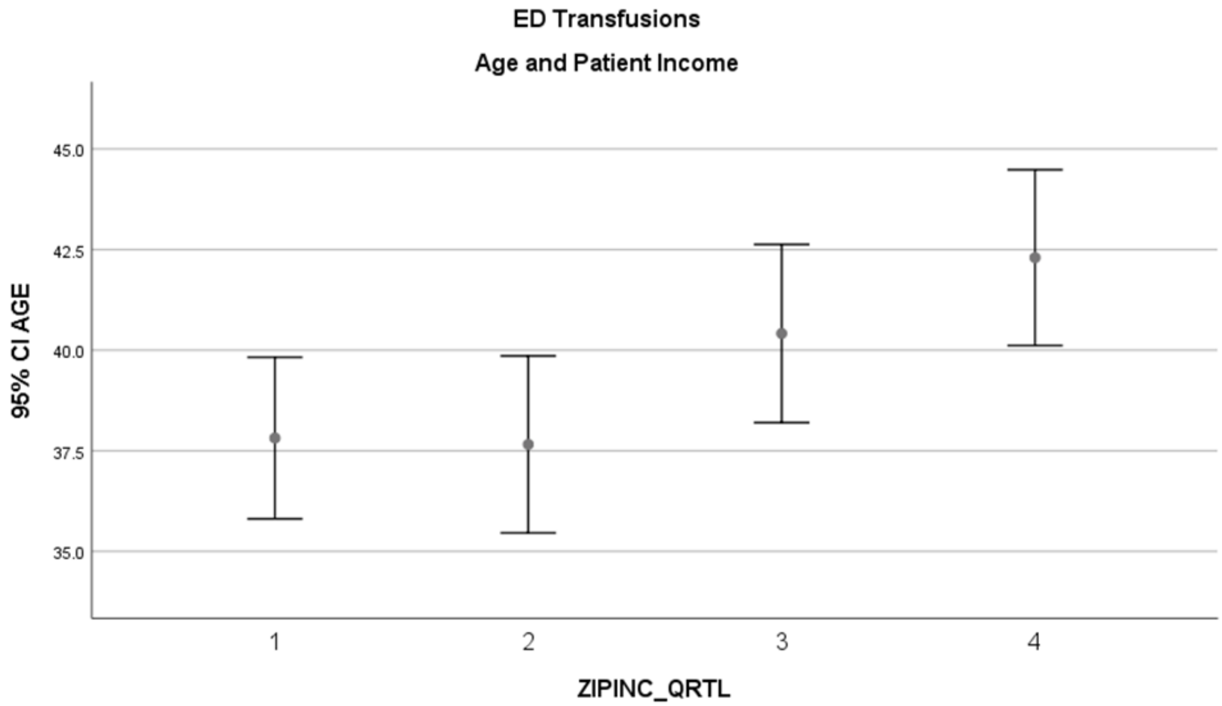
Age Distribution of Women Who Received a Transfusion in the ED



Access to interventional procedures in the ED such as a transfusion should be independent of income status. Examination of the primary payment data revealed a trend of increasing transfusions associated with great income. Those who received a transfusion were older and came from households with increasing median income, Figure 9. There were no significant differences in income proportion by frequency. When the age of each income quartile was factored in, the comparison of the highest versus lowest income quartile was significant, difference = 4.48 years (p = 0.0033 95% CI: 1.51 to 7.45).

Figure 8

ED Transfusion by Age and Median Household Income Quartile



A two contingency analysis was performed to evaluate whether primary payer was different across household income quartiles. Payer and household income were found to be significantly related, Pearson χ^2 (12, N = 331) = 28.043, p = 0.005, Cramer's V = 0.17. Follow-up pairwise comparisons between Medicaid and private insurance was performed to evaluate the differences among the proportions at each income quartile. The significant comparisons are shown in Table 21 across three comparisons, Figure 10. The Holm's sequential Bonferroni method to control for Type 1 error across the four comparisons was used.

Figure 9

Medicaid Versus Private Insurance Across Household Income Quartiles

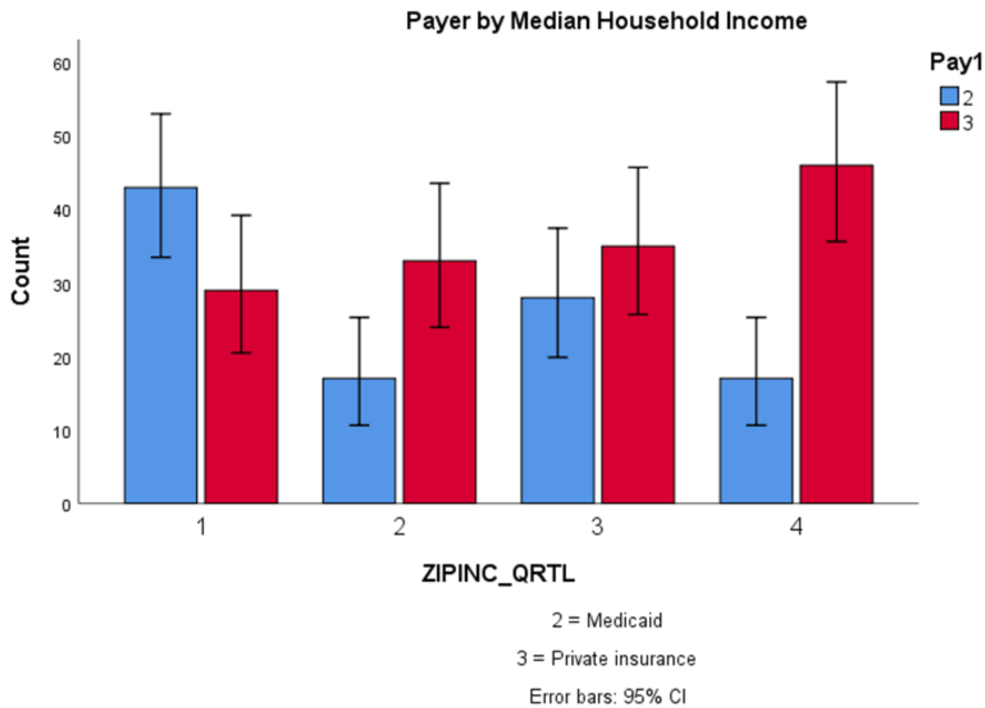


Table 19

Results From Pairwise Comparisons Medicaid Versus Private Insurance Using Holm's Sequential Bonferroni Method

Comparison	Pearson chi-square	P-value (alpha)	Cramer's V
First quartile vs the fourth quartile	14.58	<0.001 (0.05)	0.33
First quartile vs the third quartile	3.15	0.076 (0.25)	0.15
First quartile vs the third quartile	7.812	0.005 (0.017)	0.25

Hospital Admitted Cohort: Nationwide Readmissions Database (NRD)

HMB women admitted to hospital are theorized to represent a more serious health state. Comparing those admitted will address research question two. Twenty-seven states that contributed to the 2016 Nationwide Readmissions Database (NRD): Alaska, Arkansas, California, Florida, Georgia, Hawaii, Iowa, Louisiana, Maryland, Massachusetts, Mississippi, Missouri, Nebraska, New Mexico, Nevada, New York, Oregon, Pennsylvania, South Carolina, South Dakota, Tennessee, Utah, Virginia, Vermont, Washington, Wisconsin, and Wyoming. These States account for 57.8 percent of the total the U.S. resident population and 56.6 percent of all U.S. hospitalizations. All NRD states are included in the NEDS sample. To account for the smaller NRD contributing state sample, NRD results will be adjusted for the difference in US resident population, 68.7% versus 57.8%, by a factor of 1.189.

HMB admissions to the hospital was 17,894 women. The mean age of admission was 40.77 years of age. These women were significantly older than women who present to the emergency department, difference = 9.88 years, $P < 0.001$ (95% CI: -10.04 to -9.72) Figure 8. Length of stay (LOS) in hospital exhibited a wide range between 0 to 140 days. Mean LOS was 2.10 days, median 2.00 days, standard deviation of 2.20 days, Figure 11. The number of women admitted for four days or less was 95.2%. LOS was consistent across all age groups and by comorbidity, Table 22. Low back pain was excluded from this analysis as only 10 cases were recorded as a secondary diagnosis code. For low back pain, a total of 15 days of admission days were recoded with total charges of $102,299 or $6,819 per day.

Table 20

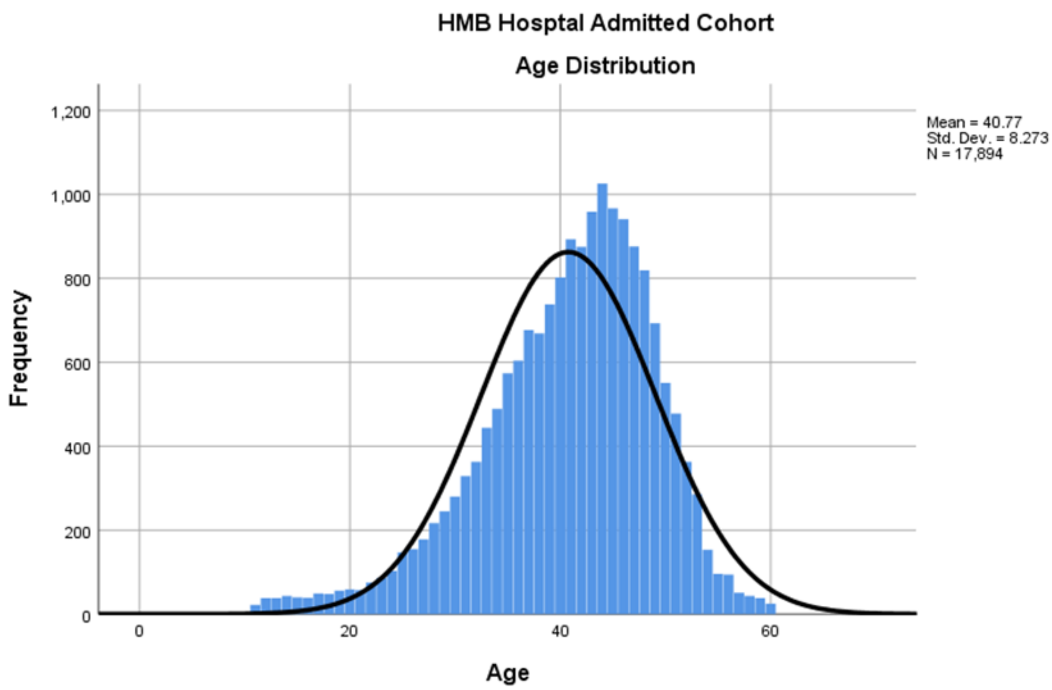
Mean LOS by Age and Comorbidity for Women With HMB Admitted to Hospital

Age		Comorbidities				
	N	Anemia N = 924	Hypertension N = 1,138	Diabetes N = 177	Headache N = 19	Depression N = 204
10-19	377	1.69	2.00*	0.5*	1.60*	1.0*
(SE)		(0.210)	(NA)	(NA)	(NA)	(NA)
20-29	1,322	1.37	1.97	2.33*	1.40*	1.50
(SE)		(0.109)	(0.161)	(NA)	(NA)	(0.374)
30-39	5,167	1.78	2.13	2.02	2.0*	1.89
(SE)		(0.059)	(0.085)	(0.19)	(NA)	(0.189)
40-49	8,851	1.83	2.01	2.05	1.6*	1.71
(SE)		(0.069)	(0.050)	(0.120)	(NA)	(0.107)
50-60	2,177	1.63	2.21	1.85	1.0*	1.79
(SE)		(0.088)	(0.123)	(0.154)	(NA)	(0.159)
Total		1.75	2.08	2.01	1.53	1.79
(SE)		(0.041)	(0.041)	(0.088)	(0.208)	(0.159)
Total LOS		1596	2340	354	29	353
Total Chrg		$29.3M	$38.9M	$6.2M	$0.33M	$7.3M

* Less than 10 cases per cell, not meaningful

Figure 10

Age Distribution of HMB Women Admitted to Hospital



The age distribution of hospitalized women with comorbidities was examined. Tables 23 and 24 compares ED versus hospitalized women by comorbidity. A secondary diagnoses of anemia, diabetes, and hypertension are summarized in Table 23. Comorbidities of headache, nausea, low back pain, and depression are summarized in Table 24. Incidence rates most comorbidities were significantly different in hospitalized women in each age group.

Table 21

Comparison Between ED and Hospital Admission (NRD) HMB Cohorts Based on Primary Comorbidities Anemia, Hypertension, and Diabetes by Age Group

Age	Comorbidity					
	Anemia		Hypertension		Diabetes	
	ED Incidence N 95% CI	NRD[1] Incidence 95% CI N	ED Incidence N 95% CI	NRD[1] Incidence N 95% CI	ED Incidence N 95% CI	NRD[1] Incidence N 95% CI
10-19	3.00 415 2.71 - 3.30	9.55* 36 6.69-13.33	0.37 51 0.27-0.48	0.27 1 0.00-1.48	0.24 32 0.16-0.33	0.53 2 0.06-1.92
20-29	2.80 1,243 2.64 – 2.96	6.51* 86 5.20-8.03	1.19 530 1.09-1.30	2.57* 34 1.78-3.59	0.46 204 0.40-0.53	0.45 6 0.17-0.99
30-39	4.52 1,261 4.37 - 4.88	4.70 243 4.13-5.33	3.29 919 3.08-3.51	4.76* 246 4.19-5.40	0.97 271 0.85-1.09	0.83 43 0.60-1.12
40-49	7.41 1,426 7.03 - 7.81	5.14* 455 4.68-5.64	5.72 1100 5.38-6.01	7.25* 642 6.70-7.84	1.35 259 1.19-1.52	1.13 100 0.92-1.37
50-60	6.38 387 5.76 – 7.05	4.78* 104 3.90-5.79	9.59 582 8.83-10.71	9.88 215 8.60-11.23	1.98 120 1.64-2.37	1.19* 26 0.78-1.75

1 unadjusted for NEDS population representation * significant difference ED versus NRD

Table 22

Comparison Between ED and Hospital Admission HMB Cohorts Based on Secondary Comorbidities Headache, Nausea, Low Back Pain, and Depression by Age Group

Age	Comorbidity						
	Headache		Nausea		Low Back Pain***	Depression	
	ED Incid N 95% CI	NRD Incid N 95% CI	ED Incid N 95% CI	NRD Incid N 95% CI	ED Incid N 95% CI	ED Incid N 95% CI	NRD Incid N 95% CI
10-19	0.54 75 0.43-0.68	1.33** 5 0.43-3.10	1.61 93 0.70-2.52	NA 0	0.35 49 0.26-0.46	0.40 55 0.30-0.52	NA** 2
20-29	0.55 245 0.48-0.62	0.38** 5 0.12-0.88	0.68 303 0.18-1.18	NA 0	0.46 205 0.40-0.53	0.33 145 0.28-0.38	1.06* 14 0.58-1.78
30-39	0.57 158 0.48-0.66	0.04** 2 0.00-0.14	0.48 135 0.41-0.57	0.08** 4 0.02-0.20	0.51 138 0.42-0.58	0.40 110 0.32-0.47	1.28* 66 0.99-1.62
40-49	0.55 105 0.44-0.66	0.06** 5 0.02-0.13	0.34 66 0.27-0.44	0.07** 6 0.02-0.15	0.40 76 0.31-0.49	0.43 83 0.34-0.53	1.11* 98 0.90-1.35
50-60	0.43 26 0.28-0.63	0.09** 2 0.01-0.33	0.21 13 0.11-0.37	0.14** 3 0.03-0.40	0.53 32 0.36-0.74	0.31 19 0.19-0.49	1.10* 24 0.71-1.64

* Significant difference, $P < 0.05$ ** Cell number too small for a meaningful comparison

*** Low back pain NRD total cohort N =10, therefore no meaningful comparisons could be made

Table 23

Incidence Rate Ratio Comparisons of Significant Hospital Admission (NRD) Versus ED

Comorbidity	Age Range	Incidence Rate Ratio	95% confidence interval	P-value
Anemia	10-19	3.19	2.20 to 4.49	< 0.001
	20-29	2.33	1.85 to 2.90	<0.001
	30-39	0.69	0.62 t0 0.77	0.009
	50-59	0.75	0.60 to 0.93	0.009
Hypertension	20-29	2.16	1.48 to 3.05	<0.001
	30-39	1.45	1.25 to 1.67	<0.001
	40-49	1.26	1.15 to 1.40	<0.001
Diabetes	50-59	0.60	0.38 to 0.93	0.0184
Depression	20-29	3.25	1.73 to 5.63	<0.001
	30-39	3.53	2.55 to 4.86	<0.001
	40-49	2.57	1.90 to 3.48	<0.001
	50-60	3.52	1.85 to 6.80	<0.001

The majority of women with HMB (95.8%) admitted to the hospital did not have a procedure performed, Table 26. The remaining patients had between 1 to four procedures performed. Of these women, 240 had a secondary diagnosis (ICD-10-CM code D50.9) of iron deficiency anemia. Their mean age was 40.06 years, median age 42.50, Figure 12.

Table 24

Core Procedures Performed on HMB Patient While Admitted to Hospital

Number	Frequency	Percent	Cumulative percent
0	17147	95.8	95.8
1	397	2.1	97.9
2	314	1.8	99.7
3	45	0.3	99.9
4	9	0.1	100.0
Total	17894	100.0	

Figure 12

Anemia Distribution Among HMB ED Cohort

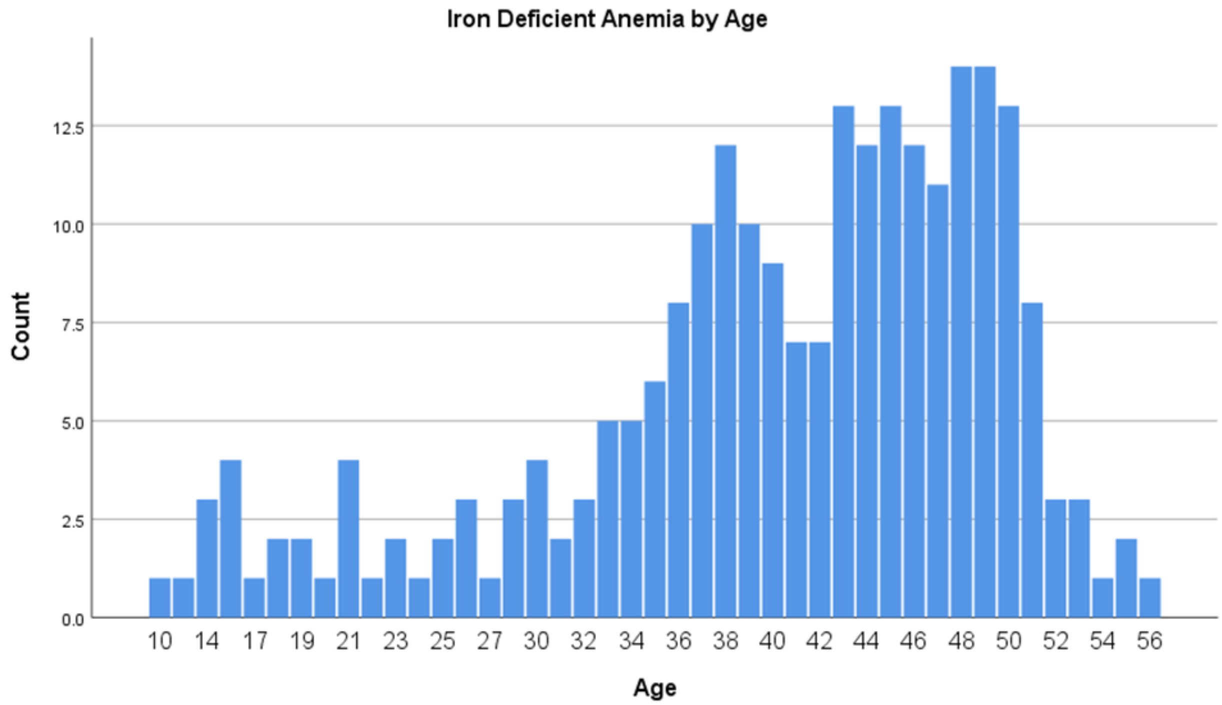


Table 25

Most Frequent DRG in Effect at Discharge Date

DRG Code	Description	Frequency	Percentage
743	Uterine and adnexa procedures for non-malignancy with complication or comorbidity (CC) / major complication or comorbidity (MCC)	9289	51.9
742	Uterine and adnexa procedures for non-malignancy without complication or comorbidity (CC) / major complication or comorbidity (MCC)	3357	18.8
760	Menstrual and other female reproductive system disorders with CC/MCC	2165	12.1
761	Menstrual and other female reproductive system disorders without CC/MCC	1454	8.1
744	D&C conization, laparoscopy with CC/MCC	839	4.7
745	D&C conization, laparoscopy without CC/MCC	509	2.8
Total		17,613	98.4

Binary Logistic Regression Model

Binary logistic regression will model the binary outcome (hospitalization or not) using categorical and continuous predictor (independent) variables. Logistic regression will predict the probability of Y materializing given known values of the predictor variable (Field, 2015). The logarithmic transformation (logit) of the linear equation addresses the assumption of independent variable linearity, Equation 4.1.

$$P(Y) = \frac{1}{1 + e^{-(b_0 + b_1X_{1i} + b_2X_{2i} + \ldots\, b_nX_{ni})}} \qquad (4.1)$$

In which b_0 is a constant, X_i is the predictor variable, and the predictor coefficient is b_i. Logistic regression uses maximum likelihood estimation to determine b_i. The logistic regression model was developed using a backward stepwise method. With the theory-driven approach, the model was developed with the aim for parsimony.

The model aimed to estimate the risk of being admitted to the hospital, based on health comorbidities present, anemia, diabetes, and hypertension. Four logistic regression models were developed. The initial model included all of the HMB cohort, N = 129,449. Variables included in the initial model included both categorical (primary payer, median household income, and patient location) and continuous variables (age). Categorical variables that did not contribute to the model and were dropped include the month of admission, weekend admission, and the quarter of the event.

Logistic regression analysis of the entire HMB cohort identified nine significant predictor variables, Table 28. Age was associated with an increase in the risk of hospitalization for each year of age. The odds ratio for age 1.091 translates to odds of being hospitalized increases by 9% per year, or approximately by 90% per decade. This is consistent with the significant difference in mean age between ED and hospitalized women. Each patient location was included in the logistic regression model, where hospitalization risk was less regardless of location. The model found that women of the middle-income quartiles were more likely to be hospitalized.

Table 26

Coefficients of the Model Predicting Hospital Admission for the HMB Cohort

			95% CI for Odds Ratio		
Included	*b*	Sig	Lower	Odds	Upper
Constant	-4.47 (-4.61 to -4.34)				
Age	0.087 (0.085 to 0.089)	<0.001	1.089	1.091	1.093
Private insurance	.47 (to 0.56)	<0.001	1.448	1.592	1.752
Large central metropolitan	-0.97 (-1.04 to 0.90)	<0.001	0.379	0.379	0.409
Large fringe metropolitan	-0.64 (-0.72 to -0.57)	<0.001	0.486	0.526	0.570
Medium metropolitan	-0.39 (-0.46 to -0.32)	<0.001	.631	0.681	.735
Small metropolitan	-0.45 (-0.54 to -0.35)	<0.001	0.588	0.641	0.700
Mirco-metropolitan	-0.29 (-0.38 to -0.20)	<0.001	0.688	0.751	0.720
Median household income: $43K-$53.9K	.090 (0.84 to 0.15)	0.002	1.033	1.094	1.159
Median household income: $54K-$70.9K	.15 (0.09 to 0.21)	<0.001	1.158	1.094	1.227

Note. R^2 = 0.121, Cox & Snell R Square = 0.127, and Nagelkerke R Square = 0.229

The logistic regression model for women with a secondary diagnosis of anemia included four significant predictor variables, Table 29. Age was associated with an increase in the risk of hospitalization for increasing age. The odds ratio for age 1.052 translates to odds of being hospitalized increases by 5% per year of age or approximately by 50% per decade. For the primary payer predictor variable only, private insurance was significant. The odds ratio of 1.58 predicts that women who were hospitalized are 58%

more likely to have private insurance. The only patient locations that were significant were large central and fringe metropolitan areas, with odds ratios 0.65 and 0.67 respectively. These odds ratios would predict a reduced risk of being hospitalized for women who live in the locations categorized as the largest. There were no significant predictors found for medium household income.

Table 27

Coefficients of the Model Predicting Hospital Admission for the HMB Cohort with Anemia Diagnosis

			95% CI for Odds Ratio		
Included	*b*	Sig	Lower	Odds	Upper
Constant	-3.14 (-3.77 to -2.51)				
Age	0.051 (0.043 to 0.059	<0.001	1.044	1.052	1.060
Private insurance	0.46 (0.07 to 0.85)	0.026	1.056	1.582	2.369
Large central metropolitan	-0.43 (-0.80 to -0.06)	0.026	0.443	0.649	0.949
Large fringe metropolitan	-.42 (-0.82 to -0.03)	0.041	0.437	0.665	0.983

R^2 = 0.068, Cox & Snell R Square = 0.077, and Nagelkerke R Square = 0.122

The logistic regression model for women with a secondary diagnosis of diabetes included eight significant predictor variables, Table 30. Age was associated with an increase in the risk of hospitalization for increasing age. The odds ratio for age 1.055 translates to odds of being hospitalized increases by 6% per year of age or approximately by 55% per decade. Women who lived in the largest three metropolitan areas were less at risk for being hospitalized. Those women with dependence on government (Medicare and

Medicaid) or self-payment was less likely to be hospitalized. No median household income quartile was a significant predictor of hospitalization.

Table 28

Coefficients of the Model Predicting Hospital Admission for the HMB Cohort with a Diabetes Diagnosis.

			95% CI for Odds Ratio		
Included	*b*	Sig	Lower	Odds	Upper
Constant	-2.45 (-3.85 to 1.08)				
Age	0.054 (0.052 to 0.056)	<0.001	1.037	1.055	1.077
Large central metropolitan	-.90 (-1.58 to -0.22)	0.012	.202	0.407	0.823
Large fringe metropolitan	-1.03 (-1.76 to -0.30	0.008	0.167	0.356	0. 167
Medium metropolitan	-.80 (-1.51 to -0.09)	0.033	0.216	0.451	0.939
Small metropolitan	-1.40 (-2.35 to -0.45)	0.005	0.092	0.246	0.657
Medicare	-1.49 (-2.57 to -0.41)	0.009	0.074	0.225	0.686
Medicaid	-0.86 (-3.37 to -0.05)	0.044	0.183	0.423	0.977
Self-pay	-1.70 (-2.74 to -0.96)	0.002	0.63	0.018	0.534

R^2 = 0.031, Cox & Snell R Square = 0.04, and Nagelkerke R Square = 0.067

The logistic regression model for women with a secondary diagnosis of hypertension included nine significant predictor variables, Table 31. Age was associated with an increase in the risk of hospitalization for increasing age. The odds ratio for age 1.048 translates to odds of being hospitalized increases by 5% per year of age or approximately by 50% per decade. Each patient location was included in the logistic regression model, where hospitalization risk was less regardless of location. Women who had private insurance or were not charged had a greater likelihood of being hospitalized, whereas those who had to self-pay had a significantly less likelihood of being hospitalized. None of the median household income quartiles was included in the model.

Table 29

Coefficients of the Model Predicting Hospital Admission for the HMB Cohort with a Hypertension Diagnosis

			95% CI for Odds Ratio		
Included	*b*	Sig	Lower	Odds	Upper
Constant	-2.44 (-3.08 to -1.80)				
Age	0.047 (0.039 to 0.055)	<0.001	1.039	1.048	1.057
Large central metropolitan	-1.04 (-1.34 to -0.74)	<0.001	0.258	0.352	0.481
Large fringe metropolitan	-0.67 (-0.99 to -0.35	<0.001	0.368	0.514	0.718
Medium metropolitan	-0.52 (-0.85 to -0.20	0.002	0.431	0.595	0.821
Small metropolitan	-0.64 (-1.00 to -0.28)	0.001	0.365	0.529	0.766
Micro-metropolitan	-0.49 (-0.84 to -0.14)	0.008	0.425	0.611	0.979
Private insurance	0.48 (0.07 to 0.89)	0.026	1.059	1.617	2.467
Self-pay	-0.91 (-1.38 to -0.44)	<0.001	0.247	0.402	0.654
No charge	1.04 (0.34 to 1.74)	0.005	1.367	2.818	5.806

R^2 = 0.069, Cox & Snell R Square = 0.079, and Nagelkerke R Square = 0.115

All four logistic regression models found age to be a significant contributor to being hospitalized, Table 32. For each year, the risk of being hospitalized increased. For the whole cohort, each decade of reproductive life increased risk by 90%. For women with anemia, hypertension, or diabetes the risk increased by 50% for each decade. These odds ratios were all significant. The interpretation of these odd ratios supports the theory that unattended bleeding in the early years of life is not without health consequences.

Table 30

Odds Ratio for Age in the Four Logistic Regression Models

Model	*b*	Odd Ratio	95% CI	*P*
Whole HMB Cohort	0.087	1.091	1.089 – 1.093	<0.001
Anemia	0.051	1.052	1.044 – 1.060	<0.001
Hypertension	0.047	1.048	1.039 – 1.057	<0.001
Diabetes	0.054	1.055	1.037 – 1.077	<0.001

Summarizing the logistic regression models for comorbidities did reveal differences in hospitalization risk. Women with private insurance regardless of the model examined were all more likely to be hospitalized, Table 33. The exception was diabetes. Women with diabetes regardless of insurance were less likely to be hospitalized.

Table 31

Odds Ratio of Hospitalization with Private Insurance

Model	*b*	Odds Ratio	95% CI	*P*
Whole HMB Cohort	0.47	1.592	1.448 – 1.752	<0.001
Anemia	0.46	1.582	1.056 – 2.369	0.026
Hypertension	0.48	1.617	1.059 – 2.467	0.026
Diabetes		NS		

Research Question 3

RQ3: What is the association between location and economic status (see Song et al. 2010) and ED presentation for HMB?

$H_0$3: There is no association between location and economic status and presentation to the emergency room for women of reproductive age in the United States.

Ha3: There is an association between location and economic status and presentation to the emergency room for women of reproductive age in the United States.

A discriminant analysis was conducted to ascertain whether location as a predictor would identify differences in the HMB cohort for the independent variables median household income, primary payer, and age. Four discriminant analyses was performed, on the entire HMB cohort, and for the three comorbidities anemia, diabetes, and hypertension. Distribution by location is described in Table 34 and Figure 13.

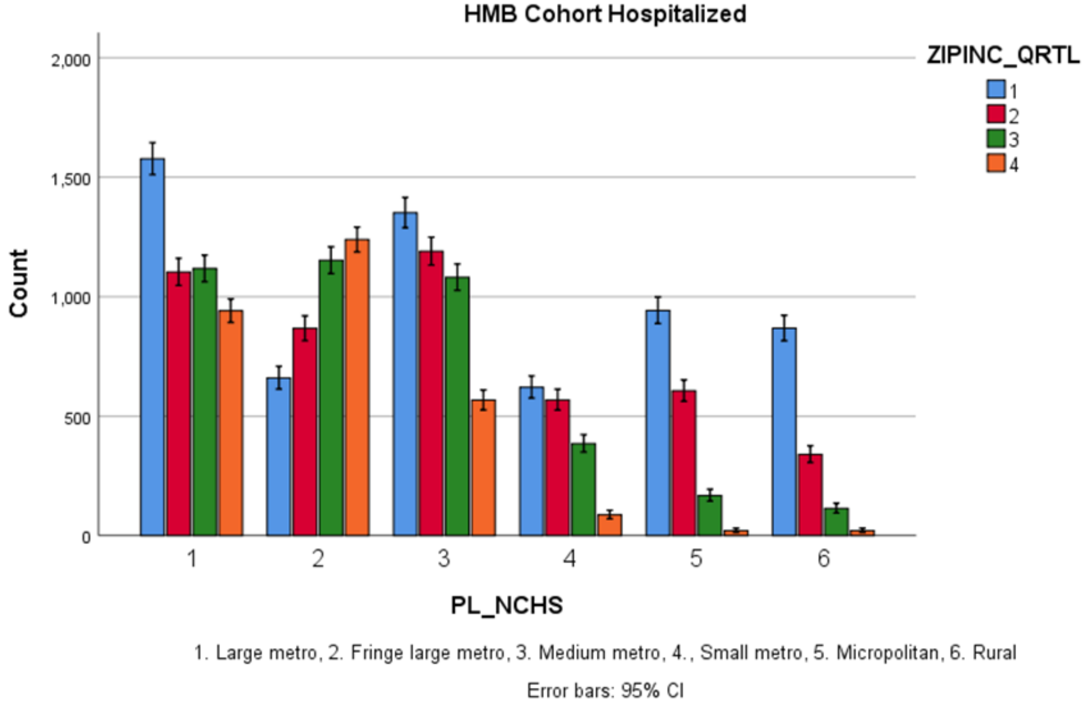
Table 32

Sample Size by Location

Location	Definition	*N*
Large central metropolitan	Central counties of metro areas of > =1 million	46,612
Large fringe metropolitan	Fringe counties of metro areas of >=1 million	27,003
Medium metropolitan	Counties in metro areas of 250,000-999,999	26,417
Small metropolitan	Counties in metro areas of 50,000-249,999	11,769
Micropolitan	Counties in metro areas of 25,000-49,000	10,702
Not micropolitan (rural)	Counties less than 24,999	6,636
Total		129,138

Figure 13

Anemia Distribution Among HMB ED Cohort



HMB Cohort

Women in the entire HMB cohort, the overall Wilks's lambda was significant, Λ = 0.889, χ^2 (15, N=127,539) = 14964.44, *P* < 0.001. Two additional functions were also significant. In addition, the residual Wilks's lambda was significant. This test suggested that the independent variables or predictors differentiated significantly among the six locations. Table 35 summarizes the within-groups correlations between the independent (predictors) and the discriminant functions.

Table 33

Standardized Coefficients and Correlations of Predictor Variables with Three Discriminant Functions for HMB Cohort

	Correlation coefficients with discriminant functions			Standardized coefficients for discriminant functions		
Predictors	Function 1	Function 2	Function 3	Function 1	Function 2	Function 3
Median income	0.999	-0.23	-0.27	.997	0.01	-0.13
Primary Payer	0.06	0.87	0.49	0.03	0.88	0.48
Age	0.12	-0.48	0.87	0.13	-0.49	0.88

Based on the coefficients, the median household income by quartile had the strongest association based on the first discriminant function. The primary payer was the strongest in the second function and age in the third. Women living in the largest urban areas (large central metropolitan, and large fringe metropolitan) (M = 0.39 and 0.61 respectively) were most likely to be admitted to hospital. The lowest median household income was the best predictor of hospitalization regardless of patient location. The percentage of women hospitalized by income and location is described in Table 36. Overall, the lowest income group was twice as likely to require hospitalization 34.2% versus the highest 16.4%, N = 6,019 and 2876 respectively. Across each location, the poorest women represented the greatest proportion of those admitted except for women living in the fringe large metropolitan regions.

Table 34

Hospitalization by Income and Location

		Median Household Income				
		$1-42.9K	$43K-53.9K	$54K-70.9K	$71K+	Total
Large central metropolitan	Count	1577	1103	1118	941	4739
	Expected	1621.9	1259.5	1082.7	775.0	4739.0
	% within	33.3%	23.3%	23.6%	19.9%	100.0%
Large fringe metropolitan	Count	660	867	1152	1239	3918
	Expected	1340.9	1041.3	895.1	640.7	3918.0
	% within	16.8%	22.1%	29.4%	31.6%	100.0%
Medium metropolitan	Count	1351	1190	1081	567	4189
	Expected	1433.6	1113.3	957.0	685.0	4189.0
	% within	32.3%	28.4%	25.8%	13.5%	100.0%
Small metropolitan	Count	621	568	385	87	1661
	Expected	568.5	441.4	379.5	271.6	1661.0
	% within	37.4%	34.2%	23.2%	5.2%	100.0%
Micropolitan	Count	942	606	168	21	1737
	Expected	594.5	461.6	396.8	284.1	1737.0
	% within	54.2%	34.9%	9.7%	1.2%	100.0%
Rural	Count	868	340	114	21	1343
	Expected	459.6	356.9	306.8	219.6	1343.0
	% within	64.6%	25.3%	8.5%	1.6%	100.0%
Total	Count	6019	4674	4018	2876	17587
	Expected	6019.0	4674.0	4018.0	2876.0	17587.0
	% within	34.2%	26.6%	22.8%	16.4%	100.0%

Determinants of health include income status and location. The median household income quartile by ZIP code indicates that this group of women come primarily from low-income settings. The lowest income category was disproportionately represented in the HMB cohort, 39.59%. All comparisons versus the next three quartiles were significantly different, Table 37 strengthening the finding that median household income is an important determinant of women's health.

Table 35

Comparisons of Median Household Income Quartiles

Median Income	$1-$42,999 Difference P value 95% CI (%)	$43,000-$53,999 Difference P value 95% CI (%)	$54,000-$70,999 Difference P value 95% CI (%)	$71,000 + Difference P value 95% CI (%)
$1-$42,999	-	13.37% <0.0001 12.69-14.05	19.97 <0.0001 19.27 - 20.66	26.30% <0.0001 25.58 - 27.01
$43,000-$53,999		-	6.60% <0.0001 5.87 - 7.33	12.93% <0.0001 12.18 - 13.67
$54,000-$70,999			-	6.33% <0.0001 5.57 - 7.09
$71,000 +				-

Anemia as a Secondary Diagnosis Cohort

The Women in the entire HMB cohort, the overall Wilks's lambda was significant, $\Lambda = 0.903$, $\chi2$ (15, N=5,569) = 565.74, $P < 0.001$. Two additional functions were also significant. The residual Wilks's lambda was significant. This test suggested that the independent variables or predictors differentiated significantly among the six locations, Table 38 summarizes the within-groups correlations between the independent (predictors) and the discriminant functions.

Table 36

Standardized Coefficients and Correlations of Predictor Variables with the Three Discriminant Functions for Anemia Comorbidity Cohort

	Correlation coefficients with discriminant functions			Standardized coefficients for discriminant functions		
Predictors	Function 1	Function 2	Function 3	Function 1	Function 2	Function 3
Median income	1.006	-0.008	0.002	0.994	-0.013	0.108
Primary Payer	0.004	0.997	0.084	0.008	0.993	0.115
Age	-0.109	-0.115	0.994	-.002	-0.084	0.996

Figure 14

Anemia Distribution Among HMB ED Cohort

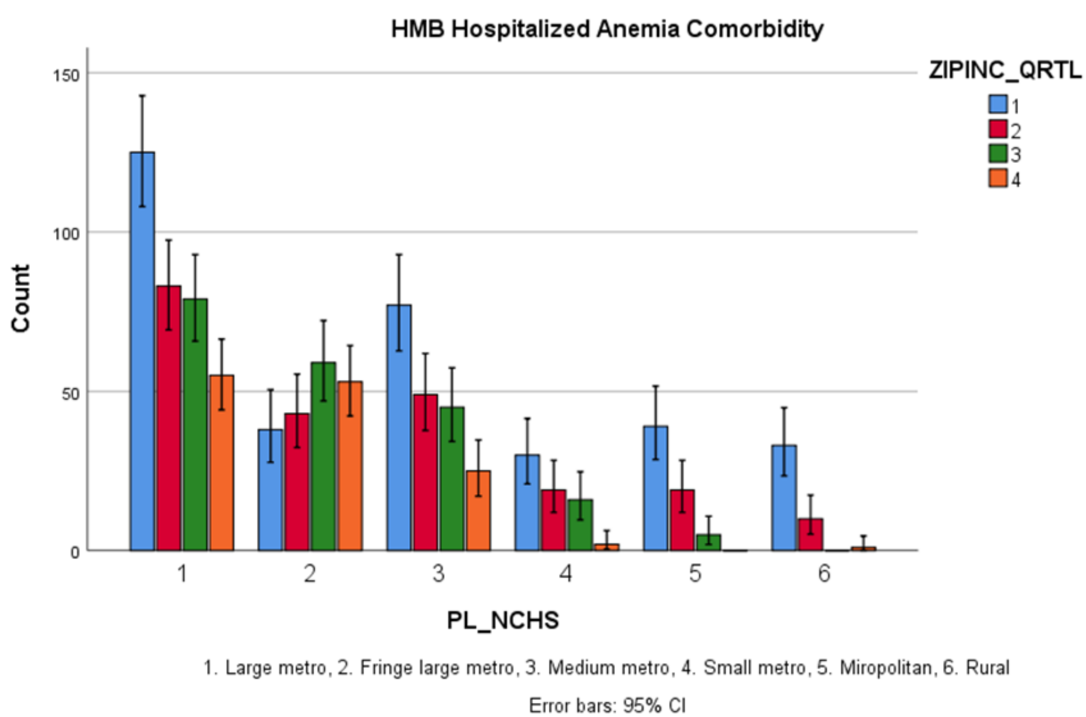


Table 37

HMB with Anemia Hospitalization by Income and Location

		Median Household Income				
		$1-42.9K	$43K-53.9K	$54K-70.9K	$71K+	Total
Large central metropolitan	Count	125	83	79	55	342
	Expected	129.2	84.3	77.1	51.4	342.0
	% within	36.5%	24.3%	23.1%	16.1%	100.0%
Large fringe metropolitan	Count	38	43	59	53	193
	Expected	72.9	47.6	43.5	29.0	193.0
	% within	19.7%	22.3%	30.6%	27.5%	100.0%
Medium metropolitan	Count	77	49	45	25	196
	Expected	74.1	48.3	44.2	29.5	196.0
	% within	39.3%	25.0%	23.0%	12.8%	100.0%
Small metropolitan	Count	30	19	16	2	67
	Expected	25.3	16.5	23.9	10.1	67.0
	% within	44.8%	28.4%	23.9%	3.0%	100.0%
Micropolitan	Count	39	19	5	0	63
	Expected	23.8	15.5	14.2	9.5	63.0
	% within	61.9%	30.2%	7.9%	0.0%	100.0%
Rural	Count	33	10	0	1	44
	Expected	16.6	10.8	9.9	6.6	44.0
	% within	75.0%	22.7	0.0%	2.3%	100.0%
Total	Count	342	223	204	136	905
	Expected	342.0	223.0	204.0	136.0	905.0
	% within	37.8%	24.6%	22.5%	15.0%	100.0%

Based on the coefficients, the median household income by quartile had the strongest association based on the first discriminant function. The primary payer was the strongest in the second function and age in the third. Women living in the largest urban areas (large central metropolitan, and large fringe metropolitan) (M = 0.34 and 0.51 respectively) were most likely to be admitted to hospital. The lowest median household income was the best predictor of hospitalization for women with anemia as comorbidity regardless of patient location. The percentage of women hospitalized by income and location is described in Table 39. Overall, the lowest income group were 2.5 times more likely to require hospitalization 37.8% versus the highest 15.0%, N = 342 and 136 respectively. Across each location, the poorest women represented the greatest proportion of those admitted except for women living in the fringe large metropolitan regions, Figure 14.

Diabetes as a Secondary Diagnosis Cohort

The Women in the diabetes comorbidity HMB cohort, the overall Wilks's lambda was significant, $\Lambda = 0.878$, $\chi 2$ (15, N = 1,052) = 136.31, $P < 0.001$. Two additional functions were also significant. The residual Wilks's lambda was significant. This test suggested that the independent variables or predictors differentiated significantly among the six locations. Table 40 summarizes the within-groups correlations between the independent (predictors) and the discriminant functions.

Table 38
Standardized Coefficients and Correlations of Predictor Variables with the Three Discriminant Functions for Diabetes Comorbidity Cohort

	Correlation coefficients with discriminant functions			Standardized coefficients for discriminant functions		
Predictors	Function 1	Function 2	Function 3	Function 1	Function 2	Function 3
Median income	0.99	-0.09	-0.05	0.99	-0.19	-0.05
Primary Payer	0.17	0.95	-0.27	0.07	0.26	0.96
Age	0.10	0.23	0.97	0.08	0.97	-0.24

Table 39

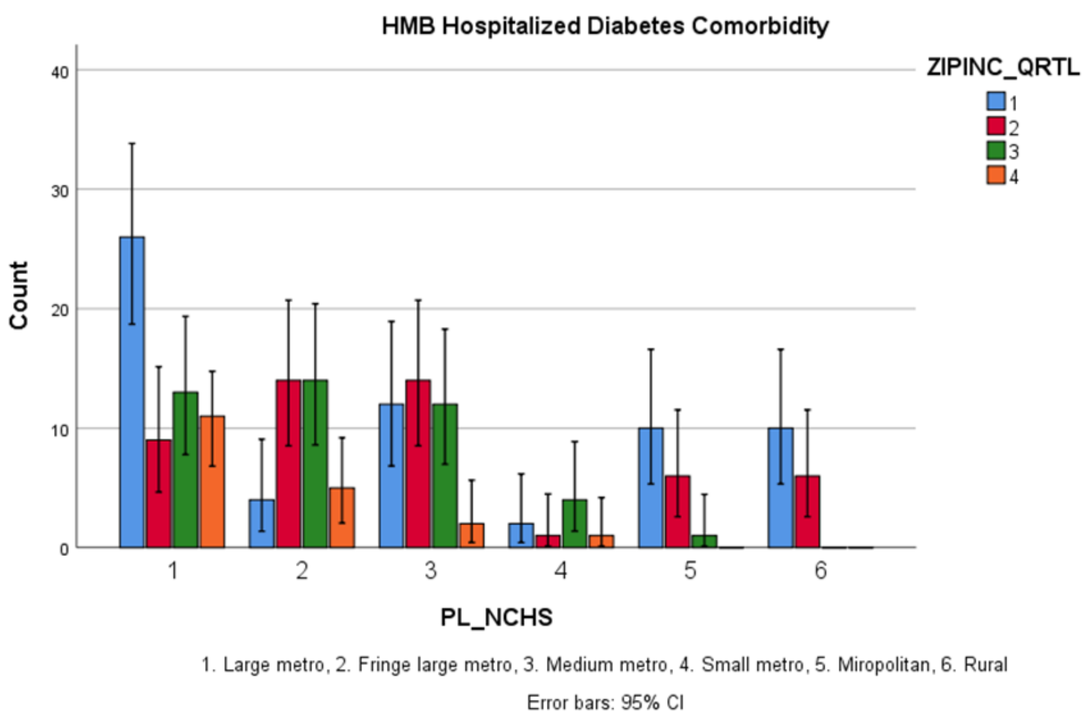
HMB with Diabetes Hospitalization by Income and Location

		Median Household Income				
		$1-42.9K	$43K-53.9K	$54K-70.9K	$71K+	Total
Large central metropolitan	Count	26	9	13	11	59
	Expected	21.3	16.7	14.7	6.3	59.0
	% within	44.1%	15.3%	22.0%	18.6%	100.0%
Large fringe metropolitan	Count	4	14	14	5	37
	Expected	13.4	10.5	9.2	4.0	37.0
	% within	10.8%	37.8%	37.8%	13.5%	100.0%
Medium metropolitan	Count	12	14	12	2	40
	Expected	14.5	11.3	9.9	4.3	40.0
	% within	30.0%	35.0%	30.0%	5.0%	100.0%
Small metropolitan	Count	2	1	4	1	8
	Expected	2.9	2.3	2.0	0.9	8.0
	% within	25.0%	12.5%	50.0%	12.5%	100.0%
Micropolitan	Count	10	6	1	0	17
	Expected	6.1	4.8	4.2	1.8	17.0
	% within	58.8%	35.3%	5.9%	0.0%	100.0%
Rural	Count	10	6	0	0	16
	Expected	5.8	4.5	4.0	1.7	16.0
	% within	62.5%	37.5%	0.0%	0.0%	100.0%
Total	Count	64	50	44	19	177
	Expected	64.0	50.0	44.0	19.0	177.0
	% within	36.2%	28.2%	24.9%	10.7%	100.0%

Based on the coefficients, the median household income by quartile had the strongest association based on the first discriminant function. The primary payer was the strongest in the second function and age in the third. Women living in the largest urban areas (large central metropolitan, and large fringe metropolitan) (M = 0.19 and 0.59 respectively) were most likely to be admitted to hospital. The lowest median household income was the best predictor of hospitalization for women with diabetes as a comorbidity for rural and micropolitan locations. The percentage of women hospitalized by income and location is described in Table 41. Overall, the lowest income group were three times more likely to require hospitalization 36.2% versus the highest 10.7%, N = 64 and 19 respectively. Across each location, the poorest women represented the greatest proportion of those admitted except for women living in the fringe large metropolitan regions, Figure 15. A note of caution in the interpretation should be exercised, as the number of patients in several of the individual cells (Table 41) are less than 10 subjects.

Figure 15

Anemia Distribution Among HMB ED Cohort



Hypertension as a Secondary Diagnosis Cohort

The Women in the diabetes comorbidity HMB cohort, the overall Wilks's lambda was significant, $\Lambda = 0.852$, $\chi 2$ (15, N = 1,121) = 679.20, $P < 0.001$. Two additional functions were also significant. The residual Wilks's lambda was significant. This test suggested that the independent variables or predictors differentiated significantly among the six locations. Table 42 summarizes the within-groups correlations between the independent (predictors) and the discriminant functions.

Table 40

Standardized Coefficients and Correlations of Predictor Variables with the Three Discriminant Functions for Hypertension Comorbidity Cohort

	Correlation coefficients with discriminant functions			Standardized coefficients for discriminant functions		
Predictors	Function 1	Function 2	Function 3	Function 1	Function 2	Function 3
Median income	1.02	-0.15	-0.03	0.996	-0.14	-0.03
Primary Payer	0.01	0.11	0.98	0.01	0.11	0.995
Age	0.00	0.11	-0.01	0.03	1.00	-0.11

Based on the coefficients, the median household income by quartile had the strongest association based on the first discriminant function. The primary payer was the strongest in the second function and age in the third. Observed patterns for the whole HMB cohort and the anemia and diabetes comorbidity were consistent. The Theory of Reasoned Action would predict that all health dimensions should exhibit a similar pattern of attention. Women living in the largest urban areas (large central metropolitan, and large fringe metropolitan, M = 0.17 and 0.68 respectively) were most likely to be admitted to hospital.

Table 41

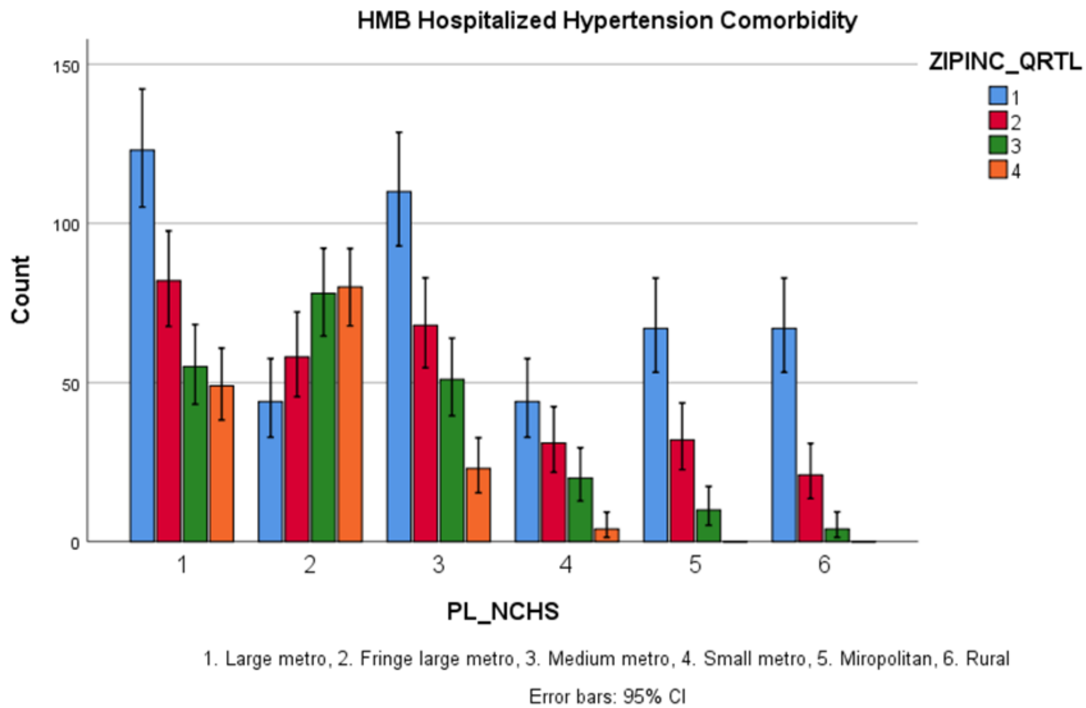
HMB with Hypertension Hospitalization by Income and Location

		Median Household Income				
		$1-42.9K	$43K-53.9K	$54K-70.9K	$71K+	Total
Large central metropolitan	Count	123	82	55	49	309
	Expected	125.4	80.5	60.1	43.0	309.0
	% within	39.8%	26.5%	17.8%^	15.9%	100.0%
Large fringe metropolitan	Count	44	58	78	80	260
	Expected	105.5	67.7	50.6	36.2	260.0
	% within	16.9%	22.3%	30.0%	30.8%	100.0%
Medium metropolitan	Count	110	68	51	23	252
	Expected	102.3	65.6	49.0	35.1	252.0
	% within	43.7%	27.0%	20.2%	9.1%	100.0%
Small metropolitan	Count	44	31	20	4	99
	Expected	40.2	25.8	19.3	13.8	99.0
	% within	44.4%	31.3%	20.2%	4.0%	100.0%
Micropolitan	Count	67	32	10	0	109
	Expected	44.2	28.4	21.2	15.2	109.0
	% within	61.5%	29.4%	9.2%	0.0%	100.0%
Rural	Count	67	21	4	0	92
	Expected	37.3	24.0	17.9	12.8	92.0
	% within	72.8%	22.8%	4.3%	0.0%	100.0%
Total	Count	455	292	218	156	1121
	Expected	445.0	292.0	218.0	156.0	1121.0
	% within	40.6%	26.0%	19.4%	13.9%	100.0%

The lowest median household income was the best predictor of hospitalization for hypertensive women regardless of patient location. The percentage of women hospitalized by income and location is described in Table 43. Overall, the lowest income group were three times more likely to require hospitalization 40.6% versus the highest 13.9%, N = 445 and 156 respectively. Across each location, the poorest women represented the greatest proportion of those admitted except for women living in the fringe large metropolitan regions, Figure 16. In the smallest two locations, the poorest women (median household income below $42,999) represented 64.6% of hospitalized patients.

Figure 16

Hypertension Distribution Among HMB ED Cohort



Summary

The inclusion criteria extracted 111,555 women with HMB from the NEDS database. From the NRD database 17,894 women were admitted to hospital. Three research questions were addressed by this study. Question one examined the association between demographic (age), health status, (anemia), insurance status and emergency department outcome (hospital admission, Y/N) for heavy menstrual bleeding. Women who were admitted to hospital were older than those who presented to the ED and were released. The older women were more likely to present with a secondary diagnosis of anemia. They had a significantly great prevalence of anemia than the general population. One-third of the women with anemia had Medicaid as their primary insurance.

Question two examined the association between health factors (comorbidities such as diabetes and hypertension) admission for menorrhagia, and emergency department outcome (hospital admission, Y/N) for heavy menstrual bleeding. The logistic regression models found age to be a significant predictor of hospitalization for all three comorbidities modeled; anemia, diabetes, and hypertension. Women with private insurance were more likely to be hospitalized regardless of comorbidity.

Research question three examined the association between location (spatial), and economic status and outcome (hospital admission, Y/N) for heavy menstrual bleeding. The lowest median household income was the best predictor of hospitalization regardless of comorbidities. Women living in the smallest rural locations with the lowest median household income were hospitalized with a substantially greater frequency than women living in larger metropolitan areas were.

Chapter 5: Discussion, Conclusions, and Recommendations

Introduction

HMB represents a physical and psychosocial challenge throughout the reproductive years. The TRA posits that the decision to address this health issue of excessive menstrual bleeding via a presentation at the ED is a health-seeking behavior initiated by profound individual concern. Analysis of the NEDS and NRD databases found a substantial number of women with HMB. The cohort identified via a presentation to the ED was N = 111,555. In the NEDS dataset, each record was assigned a weight. The weight was recorded in the core data element DISCWT. When the discharge weights were applied to the unweighted NEDS observations, the result was an estimate of the number of nationwide ED visits. Applying the weights resulted in a national estimate of 509,833 ED visits for HMB in 2016.

Hospitalized women with a primary diagnosis of HMB identified in NEDS equaled 17,894. Estimating nationwide hospitalizations for HMB translated to a probable 34,344 admissions in 2016. This rate of hospitalization is not inconsequential. Combined with the estimated half-million nationwide ED visit estimates, these counts support the premise that HMB is both an important women's health issue and a public health concern. Understanding determinants that contribute to both ED presentation and hospitalization provide context and potential opportunity for efforts aimed at reduction of the population burden.

Heavy Menstrual Bleeding Cohort Demographics

Previous reports have suggested that HMB may be more prevalent among women in their midreproductive years. An estimate of the overall prevalence in France is between 11% to 13%. This increases with age, reaching a reported peak prevalence of 24% among women aged 36 to 40 years (Marret et al., 2010). The HMB cohort who presented at the ED was aged 30.89 years (*SD* 10.37), see Figure 4. This mean age, while younger than the peak reported previously, supports the premise that women frequently wait until HMB impedes daily activities or hinders their quality of life before seeking treatment (Copher et al., 2013).

The age distribution is positively skewed, indicating an increased frequency of cases in younger women. The skewness coefficient was +0.517. The median age was 29.00, and the mode was 22 (N = 6,197) years. Kurtosis was -0.517, indicating a flatter platykurtic curve describing the distribution. An examination of seasonal distribution did not reveal patterns suggestive of higher frequency of ED presentation by a quarter of the year or month. The frequency of coming to the ED during the weekends 25.4% was lower than expected, $p < 0.0001$, (z-statistic = 11.91, 95% CI: 24.89% to 25.91%). The slight excess of weekday presentations is consistent with the theory that the ED is fulfilling a primary care function.

Ascertaining an appreciation of the overall health involved an examination of patient disposition, concurrent diagnoses, and mortality. Once in the ED, the majority of women were treated and released, 94.8%. This cohort had multiple diagnoses, with over 70% of the women having one to four additional health concerns, see Figure 5. The high frequency of multiple health problems suggests that those who come to the ED for HMB presentation carry additional health burdens. The death rate was very low, with six deaths recorded in these women. The cause of death was not available. Thus, while mortality is infrequent, the apparent health burden based on concurrent diagnoses suggests that these women may indeed delay health seeking behaviors and actions.

Determinants of health include income status and location. The median household income quartile by ZIP code indicates that this group of women comes primarily from low-income settings. The lowest income category was disproportionately represented in the HMB cohort, 39.59%. All comparisons versus the next three quartiles were significantly different, see Table 37. The majority of these women lived in large metropolitan locations. Those living in locations classified as metropolitan represented 58.71% of the cohort. Those living in rural settings or micropolitan (small to medium-sized towns) represented 12.61% of the study population. Understanding the reasons for this disproportionate distribution was not possible. When looking at the entire 2016 NEDS population where the location was reported (missing data excluded; N = 32,508,694), 16.00% of the ED cases came from rural and micropolitan regions. The contribution of large metropolitan regions was 54.51%, slightly less than the HMB cohort.

Economic costs associated with ED visits are not trivial. The median charge was $2,486 (range $100 to $127,317). The mean cost was $3,373, and the mode was $2,150. For this cohort total, ED costs recorded was $325.8 million. For comparison, the median cost for the entire NEDS 2016 population (N = 27,930,718) was $2,007, the mean was$3,359, and the mode was $1,303. This suggests that these patients incurred slightly greater costs than other patients who present at the ED.

Research Question 1

The association between demographic (age), health status (anemia), insurance status, and ED presentation for HMB was examined to ascertain the impact of chronic blood loss manifested as anemia. Anemia was extracted as a secondary diagnosis using the ICD-10 code D64.9. The filter identified 4,731 (4.24%) HMB women with a secondary diagnosis of anemia. The frequency of anemia increased with increasing age, see Figure 6. The mean age of this group was 34.81 years (*SD* = 10.83). The mean difference versus the whole HMB cohort was 3.92 years, which was significantly different, $p < 0.0001$ (95% CI: 3.62 to 4.22). The greatest incidence of anemia was in women aged 40 to 49 years, 7.41%. The null hypothesis ($H_0 1$) was rejected: There is no statistically significant association between demographic factors (age), health status (anemia), insurance status, and presentation to the emergency room for women of reproductive age in the United States.

Women with anemia used primarily three forms of insurance. Medicare, private insurance, and self-pay represented 92.67% of the primary payment used. There were significantly more women on Medicare versus the other insurance. The differences between women whose primary payment was Medicare (38.10%) were significantly different greater than private insurance (34.26%), difference 3.84%, and $p = 0.0196$ (95% CI: 0.61% to 7.05%). A significant difference was also observed between Medicare versus self-pay (30.47%), difference 7.63%, $p < 0.0001$ (95% CI: 4.35% to 10.87%). The difference between private insurance and self-pay 3.79% was also significant, $p = 0.025$ (95% CI: 0.47% to 7.09%).

In addition to testing the hypothesis via ANOVA, further support for the H_a1) was found when the HMB cohort was compared to a recent analysis of the NHANES 2016 (Le, 2016) cohort of women, see Table 15. The anemia prevalence between NHANES and the HMB was significantly different in the three oldest age groups. The TRA posits that women seeking health support in the ED have accrued a substantial physical and psychosocial burden. Anemia as a sentinel health marker for chronic blood loss was expected to be more prevalent among women with HMB. The findings that age is associated with a greater frequency of anemia supports the theory that there is an accumulation of health deficits over time. Combined with a significantly greater Medicare presence, this suggests economic disadvantage among women who present at the ED.

Research Question 2

Several health factors may be important determinants associated with HMB. Comorbidities such as diabetes and hypertension were selected as broad health indicators for general wellness. Specific comorbidities for HMB including headache, nausea, low back pain, and depression were also examined for their contribution to ED presentation for HMB. I examined the hypothesis that there is no association between health factors (comorbidities such as diabetes and hypertension) and presentation to the emergency room for women of reproductive age in the 30 states participating in the NEDS United States. The frequency of these comorbidities is listed in Table 18. Physical comorbidities headache, nausea, low back pain, and depression were all infrequent, less than 0.5% of the secondary diagnoses of these women. This low rate was unexpected but maybe a reflection of an ED provider being focused on the primary symptom at presentation. A comparison of the comorbidities incidence in the ED and treat and release cases with women admitted to the hospital is summarized in Table 22 and Table 23. These tables also summarize the comparisons for each comorbidity by age strata. As tabulated in Table 24, women in the youngest age categories were more likely to be admitted to the hospital. This was most pronounced in the youngest age category of 10 to 19 years, with an incidence rate ratio of 3.19, $p < 0.001$ (95% CI: 2.20 to 4.49). This may be a reflection of more intensive treatment for adolescent girls versus older women. Exploring the association between age in women with blood loss, three important surrogate markers were examined: anemia, iron deficiency, and those who received a transfusion. The association revealed a progressive and significant increase in each blood loss category by age (versus the whole cohort), see Table 20. This supports the findings that the hematological burden of heavy periods accumulates over reproductive years.

Diabetes did not appear to have a strong association in either ED presentation ($N = 841$, 0.75%) or hospitalization ($N = 177$, 0.99%); the difference was not significant. The theory of overall poor health associated with delayed health-seeking behavior was not evident with this comorbidity. A potential explanation is a bias towards documenting the primary complaint. Additionally, diabetes is a chronic condition, so unless a patient is in crisis, they would likely not be recorded in the presence of an excessive bleeding event.

Hypertension was associated with hospitalization in women ages 20 to 49. Across the three age strata (20-29, 30-39, and 40-49), women hospitalized were significantly more likely to be hypertensive than women who were treated and released from the ED. This comorbidity was more prevalent in the HMB cohort, *N* = 3,194 (2.86%) than diabetes. The near four-fold difference suggests that this comorbidity might be a better measure of wellness than diabetes.

To assess risk associated with comorbidities, a logistic regression model was developed using a backward stepwise method. A primary aim was to estimate the risk of being admitted to the hospital based on health comorbidities present, anemia, diabetes, and hypertension. The model was developed with the aim of parsimony. This resulted in trimming the variables included in the primary payer, median household income, and patient location (categorical) as well as age (continuous). Four models were run: for the HMB cohort (*N* = 129,449), anemia (*N* = 6,328), hypertension (*N* = 5,535), and diabetes (*N* = 1,199).

All four logistic regression models found age to be a significant contributor to being hospitalized, Table 32. For each year, the risk of being hospitalized increased. For the whole cohort, each decade of reproductive life increased risk by 90%. For women with anemia, hypertension, or diabetes the risk increased by 50% for each decade. These odds ratios were all significant. The interpretation of these odd ratios supports the theory that unattended bleeding in the early years of life is not without health consequences.

The regression models found signals associated with both patient location, type of insurance, and median household income. In the overall HMB cohort, women who lived in large metropolitan areas were less likely to be hospitalized, odds ratio of less than 1.0. This would suggest several possible potential explanations. First, women who live in large metro areas may have access to specialized care that may mitigate the severity. Second, in large metro areas, ED services may be sufficiently comprehensive to result in a greater proportion of women to be treated and released. Women with private insurance regardless of the model examined were all more likely to be hospitalized, Table 33. Interestingly, in the diabetes comorbidity model, women with Medicare as their primary insurance coverage were 42% less likely (Odds ratio = 0.423) to be hospitalized (p = 0.044, 95% CI: 0.18 to 0.98). This may indicate a bias towards insurance coverage, financial capabilities, or overall economic resources. Finally, higher household income quartiles were consistently more likely to be hospitalized. These findings support the theory that while access barriers to the ED may be low, those who are admitted require greater economic resources to gain access.

The null hypothesis that there is no association between health factors (comorbidities such as diabetes, and hypertension) and presentation to the emergency room was rejected. Women are at greater risk for hospitalization as they age during reproductive years. Those with higher income and private insurance also appear to receive more intensive care as assessed by hospitalization risk. These findings support the theory that health avoidance behavior increases health burden and that in later life a tipping point for action is reached.

Research Question 3

Exploring the association between patient locations as a surrogate for diagnostic intensity was the final analysis. The theory posits that women located in larger metropolitan areas may have greater resources available to them. This will include specialized providers' who will be able to provide expert care and be able to make accurate diagnoses in the face of excessive bleeding symptoms (Song, et al. 2010). This research question further explores the association between location and presentation to the emergency room for women of reproductive age in the USA.

As a follow up to the significant findings in research question one, discriminant analysis was used to predict if the location (grouping variable) with independent variables, primary payer, median household income, and age predicted hospitalization. Women who were hospitalized in the HMB cohort were most likely to live in large metropolitan areas. These areas are defined as having populations greater than 1 million people. Low median income was also a significant predictor of hospitalization. The proportion hospitalized in the lowest household income group was significantly greater versus each of the other three quartiles, $p < 0.001$. Women living in the smallest locations (population less than 25,000) and with the lowest household income had the highest proportion of hospitalizations among this cohort, Table 36. Additionally, transportation barriers may also contribute to women delaying seeking medical care (Wolfe et al., 2020). This finding may suggest that in the rural locations where transportation barriers are greater for poor women and expert care may be limited or not available, treatment in the ED may not be sufficient to release these women, Figure 13. In the rural location

64.6% of the low-income (zipinc_qrtl 1) women were hospitalized, double the expected rate. These findings support the premise that women in areas of limited access to expert care may be either initially undertreated, or they will delay seeking care until the symptoms become more serious.

Figure 13 illustrates the finding that there is an increased likelihood that women who live in the lowest median income quartile were more likely to be hospitalized regardless of location. One exception to this trend is found in fringe metropolitan locations. A potential explanation of this finding that the fringe metropolitan locations are an outlier in this trend could be that these areas, expected to be mostly suburban, may have an income distribution bias due to the higher cost of living in these urban locations. Examining Table 36 reveals that in this geographical location Zipinc 1 represents the fewest cases (16.8%). However, this income stratum represents the largest segment, 39.59% of the total HMB population (Table 12). The smallest geographical areas appear to have a disproportionate number of low-income women requiring hospitalization. This supports the premise that place matters. Women with heavy menstrual bleeding who live in poverty and in rural settings may have the fewest options for early corrective therapies such as hormone replacement (contraceptives) or anti-fibrinolytic options. The consequence is that health-seeking behaviors are delayed to the point where ED interventions may not be effective, and hospitalization is more frequently necessary.

Anemia

Exploring the HMB cohort with a secondary diagnosis of anemia found a similar trend with the overall HMB cohort. The interest in women with a confirmed secondary diagnosis of anemia is that this additional health burden is directly associated with prolonged and chronic blood loss. Anemia is a late-stage indicator of iron deficiency, one of the most common nutritional deficiencies in the United States (Sekhar et al., 2017). From the TRA, women who avoid seeking health for lengthy periods are expected to develop secondary complications including anemia (Karlsson et al., 2014). This sub-group demonstrated the same trend seen in the overall HMB cohort, a disproportionate rate of hospitalization based on income across all locations except the fringe metropolitan areas, Figure 13. In the rural area, 75% of all hospitalizations were in the lowest median income stratum.

Overall, the lowest income group were 2.5 times more likely to require hospitalization than the highest income stratum, 37.8% versus the highest 15.0%, N = 342 and 136 respectively. The 22.8% difference between these two groups is significant ($p < 0.0001$, 96% CI: 14.2% to 30.1%). Women in the lowest income stratum also appear to have a more serious health phenotype. While the association of increasing age in women, who present with anemia, supports the theory that delayed health-seeking behavior increases the health burden, hospitalization is highest among the youngest women, table 25. This trend to treat the younger women more aggressively may be due to a treatment bias for younger women or be due to a lower threshold for interventions based on age. The anemia sub-population follows the overall HMB cohort trend of a health disadvantage being associated with their location (place).

Diabetes was explored as one of two determinants of overall health. Diabetes represented a small segment of the HMB cohort, 0.75%. The analysis should be interpreted with caution due to the low statistical power. Based on the CDC (National Diabetes Statistical Report – CDC, 2018) crude population prevalence estimate for women aged 18 to 44 is 3.0% (95% CI: 2.6 to 3.6), this comorbidity appears to be underrepresented. The incidence in the age groups 20-29, 30-39, and 40-49 were 1.37%, 1.78%, and 1.8% respectively approximately half of the expected rate. A possible explanation could be that in the emergency department, the clinical focus on the primary complaint may lead to a bias to not collect complete health information especially if health factors are considered extraneous to the primary reason for presentation. Additionally, if women do not report their complete health history and wish to focus on the bleeding, health comorbidities such as diabetes may be under-reported.

Examination of Figure 14 reveals a similar trend observed in the overall HMB cohort. Inferring differences between locations is not possible due to the very small numbers in the smallest locations. The overall comparison between women in the lowest median income group versus the highest was significant. The income lowest stratum represented 36.2% (N = 64) of the women versus the highest-income 10.7% (N = 19). The difference of 25.5% was significant, p = 0.035, 95% CI: 2.0 to 40). No other income comparisons were statistically significant.

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Hypertension

Hypertension was the second health determinant studied as potential comorbidity that could also be associated with poor health-seeking behavior. Women with a secondary diagnosis of hypertension represented 2.86% (N = 3,194) of the total HMB population. The trend of increased hospitalization frequency among women with the lowest median income persisted, Figure 16. At each location again except for fringe metropolitan regions, women in the lowest income stratum were significantly more likely to be hospitalized. A woman with HMB and hypertension in the lowest income stratum was 2.9 times more likely than the highest income group to be hospitalized. This difference of 26.7% was significant, $p < 0.001$ 95% CI: 19.0% to 33.2%. Consistent with findings of the whole HMB cohort, the influence of the determinant income in women with a secondary diagnosis of hypertension is associated with greater hospitalizations regardless of place. Also, the poorest women in the smallest locations, rural and micropolitan dominate hospitalizations.

Strengths and Limitations

The study was retrospective in design, involved creating an inception cohort from the 2016 HCUP NEDS and NRD databases. The HCUP data is a secondary data source and is limited to the data captured in the available record. This research used the case definition for HMB based on The International Statistical Classification of Diseases and Health Related Problems, ICD-10-CM/PCS codes. The primarily patient selection was consequently dependent upon the case report classification by the attending physician. Verification of the accuracy of the initial diagnosis is not possible, as patient identification protection does not permit any form of back tracing of cases. The cases thus extracted from the databases are considered valid as they were coded for HMB and all associated hospital costs were paid for via Medicare, Medicaid, private insurance, or out of pocket sources. The possibility of an inaccurate diagnosis of HMB, in any case, cannot be ignored.

A woman entering the ED with the complaint of HMB will not be able to receive a definitive test to confirm the historically accepted daily blood loss of greater than 80 mL per menstrual cycle (Hallberg, & Nilsson, 1964). Thus, an attending physician will rely primarily on the patient reported concern in classifying the primary diagnosis. Subjective and self-reporting of blood loss may be considered a poor indicator of actual menstrual loss. Quantifying monthly blood loss is challenging, precise reporting of blood loss is more problematic (Moon et al., 2017). Evidence does indicate a positive correlation with objectively measured blood loss (Quinn, & Higham, 2016). A caveat is that the positive predictive value is low. The validity and strength of patient or self-reported events is gaining interest and credibility (O'Mahony et al., 2016). While individual perceptions may be prone to high degrees of variability, patient's reported outcomes (PRO) data are useful when large sample sets are available to represent community health (Begg et al., 2013). This research thus relied on the collected cases based on the patient reported complaint of HMB. These limitations notwithstanding, PRO data may contribute to a more complete and deeper understanding of the true population burden and provide insights into the impact of living with a disease (O'Mahony et al., 2016). Thus, the estimates of risk and determinants associated with HMB have a reasonable level of evidence for public health consideration.

Understanding the population burden of HMB requires a large data sample to provide evidence that is potentially externally valid. A key strength of the National databases used is a large number of contributing centers. In the NEDS database where 111,555 HMB cases were extracted from 32,677,936 records, 953 hospital EDs from 36 states contributed data. This NEDS sample represented an approximately 20% stratified sample of US hospital emergency departments. Weighted for National estimates, the number of ED visits represents approximately 144,842,742 visits. A strength of so-called big data is the reduced variability and the influence of individual center effects (Kafadar, 2020). Additionally, with a large data set the violation of the independence of each event is unlikely (Murray et al., 2020). While having greater visibility of the individual patient record would be ideal, the ability to generate estimates of contributors to HMB presentation in the ED is greatly facilitated by these large national data sources.

A limitation associated with secondary data is that the data fields collected are defined by the lowest common denominator. This limitation illustrates that many of the states do not report racial data. As a result, no racial data was available in this national database. If an exploration of racial differences or disparities was to be pursued, only the individual state databases that report race could be queried. Such an analysis would not provide a national picture undermining the intent of this project. Another limitation of the individual data provided was an absence of information on height and weight to allow for BMI estimation. The Theory of Reasoned Action posits that women who exhibit prolonged health avoidance behavior regarding their reproductive health to need ED attention may also have other comorbidities such as a greater prevalence of obesity and smoking. Unfortunately, these determinants as well as educational attainment were not available.

Threats to Validity

The collection methods and input integrity of the HCUP data as a secondary data source are important determinants of the quality of the findings. Thus, a key threat to validity is to use data for research purposes for which they are not specifically generated

(Kuriyama et al., 2017). The NEDS and NRD data were collected from contributing hospitals. The rigor of the collection methods and accuracy has been demonstrated through over a decade of collection. A primary element of the validity of these research findings will be the accuracy of the disease status coded into the electronic records in which rely on the categorical codes of ICD-10-CM/PCS. Studies that have compared diagnoses and procedures reported in administrative data compared with medical records have found acceptable levels of agreement (Casey et al., 2016). Hsu et al. (2014) found that the positive predictive value (PPV) for the ICD-9 code 471.x for nasal polyps was 85%. This would support the premise that those with the diagnostic code do indeed have the disease. More recent data on HMB bleeding where ICD-10 codes have been cross-referenced with the patient files support the premise that these secondary records can be considered valid for the diagnoses categorized (Borzutsky, & Jaffray 2020).

Internal Validity

Generation of reliable risk estimates from the HCUP data will require addressing bias, confounding, and random error as alternative explanations (Casey et al., 2016). While large sizes reduce the bias due to random error, bias due to measurement error is independent of sample size (Mooney et al., 2015). Estimation of measures of the association has been quantified with 95% confidence intervals. Uses of hospital records have limitations including data collection and misclassification bias. The ICD-10-CM/PCS coding has to be assumed to be correct as there is no possibility of back tracing patients to validate accuracy. Attrition bias is not expected to be a concern as each ED presentation is recorded over 90% of cases were presented and released within one day.

The motivation to seek care in the ED is theorized to be driven by high degrees of symptom severity minimizing the attrition effects in individuals with access and also strengthen the likelihood of accurate disease coding.

Several biases should be examined. Nonparticipation bias remains a concern as this is expected to result in underestimation of the overall population problem, and potentially skew the study population towards individuals with higher income, educational attainment, and access to health care resources. Individuals who choose not to seek care are theorized to have symptoms that may be deemed non-severe or having minimal impact on the quality of life. The income distribution in the HMB cohort would suggest that nonparticipation bias is limited, table 12. The lowest median household income quartile ($1 – $42,999) represented 39.59% of the inception cohort, the greatest proportion. The highest quartile (> $72,000) represented the smallest proportion of the cohort, 13.29%. Recall bias is likely minimal as the data is generated by the extraction of individual patient billing records collected at the time of ED presentation. Lastly, statistical regression is likely minimal due to the large sample size. Confounding by extraneous effects such as age and other factors such as medium income quartile, location, and payer were examined and adjusted for. Confounding by indication and severity are important. The presence of symptoms (indication) is the selection criteria for inclusion. Each HMB event is coded and recorded with no context of individual impact or health burden. A spectrum of severity of symptoms was captured in each ICD-10 coded event, with no ability to discriminate between benign and severe bleeding events. This study used the criteria of hospital admission as a surrogate for either severe symptoms requiring additional complex management or a compromised health state that requires additional support. In either case, hospital admission from the ED was considered to represent severe or poor health status.

Random error due to inaccurate HMB classification was minimized. The cohort was assessed by screening the study population data for errors such as a male being coded for HMB. Elimination of records containing men presenting with HMB was done to create the final study cohort. Additionally, the inception cohort only contained reproductive age: older than 10 years on the bottom and below 65 years were on the top.

Interpretation of the analysis should keep in mind several limitations. First, the data is sourced from administrative records and does not provide information on elements that may influence outcomes such as resources within a hospital, staffing, protocols, and the infrastructure. These inputs may contribute to the interventions utilized and admission decisions. Detailed data on individual patient management are also not available. This research cannot determine the overall health burden associated with HMB presentation.

Generalizability

External validity is concerned with the degree to which an observed association between an intervention and the reported results may be generalized to four distinct domains of variation: people, interventions, outcomes, or settings (Huebschmann et al., 2019). An important contributor to external validity is the representativeness of the observed population and the settings of the study. This project was designed to explore the ED as the setting for women who have found bleeding events to be either too severe or too frequent to be considered normal. Evidence suggests that the ED is often the place of last resort for individuals who lack access to healthcare providers or who may be in an acute crisis (Sardo et al., 2016). This study was not designed nor able to identify the root causes or reasons for ED presentation. The methodology utilized was to collect HMB ICD-10 coded cases, and describe, and estimate risks based on available data for this inception cohort. How representative the women identified are for all women with HMB is difficult to characterize.

From the studied inception cohort, women who were hospitalized for heavy menstrual bleeding symptoms were older with a mean age of 40.77 years (SD 8.27). This finding was consistent with a large study by Morrison (2008). Morrison et al. found that women who were hospitalized for excessive bleeding had a mean age of 42 years. They also reported that women between 25 to 50 years represented 85% of the study population.

The generalizability of the findings should be interpreted with caution. The HMB inception cohort is a sub-set of women who likely experience regular excessive monthly bleeding. The reported median age was 29.00 years (standard deviation of 10.37 years, figure 4) interquartile range 16 years (IQR = 21 – 37). The positive skewing suggests that many of the women who present at the ED are in the younger range of their reproductive years. Women from the lowest income stratum dominated this cohort. They were equally likely to have Medicare or private insurance. A claims-based retrospective study of idiopathic (no underlying condition identified) HMB women who were enrolled in a large US health plan, extracted 21,362 women with a mean age of 39.42 (SD 6.78) years

(Copher et al., 2013). Thus, women with access to healthcare may be able to receive supportive treatment in the early years and delay symptoms that are more serious until later years. This would suggest that the younger cohort of women who use the ED might not have healthcare options in the early reproductive years available to those with health care insurance. The generalizability of this HMB cohort to the entire population may need to be held in the context of both access to healthcare (insurance status) and income. Both of these determinants are related.

A notable gap in the secondary data set is the absence of information on any other care associated with the primary diagnosis. Women who find that the ED is their refuge for a bleeding event perceived as excessive are not expected to have routine access to gynecological or expert care. HMB cases present frequently in gynecology offices (Davis, & Kadir, 2017). Such cases with access to health care would likely be attended to in the physician's office or clinic. The HCUP databases do not capture such visits. These HMB visits collected in NEDS and NRD will be limited to those seeking attention in an ED and thus represent women with either limited resources or inadequate access to specialized care. The study sample thus represents the more serious or troublesome HMB events and should be considered as an estimate of the more serious bleeding events in the community, thus limiting the external validity of these findings. Mild bleeding events are theorized to not reach a sufficient threshold to initiate a health-seeking behavior and thus remain undetected.

Public Health Concern

Women who present with complaints associated with excessive menstrual bleeding may represent a group who suffer in silence. This research project was designed to take the observations from the HCUP databases NEDS and NRD and translate them to communities, T4. While the results presented from the inception cohort provide a national perspective, the findings of morbidity and burden are from individual women thus supporting the adage and reminding one that all public health is local (Green et al., 2020). From the extraction of HMB cases and the national weighting, an estimated half a million women (509,833) nationally present at emergency departments for heavy menstrual bleeding. Of these presentations, 6.74% require admission to the hospital (34,344). Many of these women (39.59%) come from households with the lowest median income quartile of less than $43K per annum, supporting the theory that the ED is for many women a healthcare refuge. The findings from this research quantify the considerable public health issue associated with this silent burden.

Quantification of the burden of disease is limited to the associated hospital charges. Based on the hospital charges (Table 13) for each HMB presentation, the estimated national cost impact is in the range of $1.7 billion annually. The psychological weight and consequences for each woman not available from this data. The Theory of Reasoned Action posits that a woman who presents in the ED with HMB may be initiating health-seeking behavior for many reasons. The perceptual framework of reproductive health is complex. Health-related challenges might range from personal restrictions that lead to work interruptions, reduced educational attainment, and self-limiting socialization. A recent qualitative study on the impact of HMB in adolescent girls (aged 13-19) identified several themes of importance. The coordination of healthcare visits, coping day-to-day, school attendance, and the need for information (Li et al., 2020). Interviews with their parents recognized four important themes from the interviews: (1) interactions with healthcare providers, (2) a need for greater information on reproductive biology, (3) support and acceptance that the concerns are real, and (4) the financial impact from repeated healthcare visits (Bellis, et al. 2020). These reports coupled with the estimated cost impact support the finding that the public health burden associated with HMB may be underestimated.

From a social change perspective, patients who are compelled to seek treatment at an emergency department represent a cohort who have most likely found symptoms to be persistent or acutely problematic beyond their perceptual norm. These presentations at the ED must be recognized as serious in nature. The number of women presenting with a single diagnosis was 28.4%, Figure 5. The converse is that 71.6% of the women had more than one comorbidity diagnosed at presentation. This finding further adds context to the health burden that is associated with HMB and would be expected from women who have delayed seeking health. From a public health perspective, the argument for paid sick leave may reduce the need for ED presentation. Schneider (2020) showed that employees without sick leave are more likely to forgo needed medical care. Such delays in seeking health care are expected to exacerbate existing conditions and lead to more consumption of health care resources.

Estimation of a significant risk for hospitalization for age by the logistic regression model supports the theory of accumulating burden of reproductive life. This is not proof of a causal association. These findings from secondary data should be interpreted with caution, and be considered hypothesis-generating. This inception cohort may best represent women who due to circumstances of delayed health-seeking behavior have turned to the ED department for a health crisis. Additionally, this use of the ED may be a feature of the US medical healthcare model and not generalizable to countries with comprehensive care and greater access to specialized care. The reported HMB events as coded by ICD-10 categorization is considered a useful indicator of a true HMB event. Thus estimation of risk and cohort descriptive statistics allow for a characterization of the public health burden associated with unattended HMB in the community.

HMB may have several potential causes and downstream consequences. Beyond the rising risk of more profound anemia, hospitalization, psychosocial and quality of life effects, other elements of reproductive health may also be affected (Yu et al., 2020). Maternal mortality has been described as a crisis in the US (Mullen, 2020). In 1986 according to the CDC, seven women died during childbirth for every 100,000 live births (Cohen, 1987). In 2016, the number has increased to 17 per 100,000 live births. Examining the two periods of highest maternal risk for death: day of delivery and days one to six postpartum, the number one cause of death during both times is hemorrhage, 24%, and 18% respectively (Mullen, 2020). While the data is not available, a suspicion that many of these women may have had HMB symptoms in early life seems reasonable. Further evidence supporting the theory that HMB is a sentinel event indicating potential underlying health issues is found in a report by Zia et al. (2020). Their prospective study followed 235 consecutive postmenarchal adolescents who were referred to a bleeding disorders clinic for HMB. Of these referrals, 33% were diagnosed with a bleeding disorder. The authors found a high prevalence of a blood disorder independent of the bleeding pattern. Of these adolescents who presented at the ED, 55% presented with anovulatory bleeding which was considered difficult to manage. Additionally, adolescents who presented at the ED were more likely to be hospitalized (OR = 2.03, p = 0.072) and more likely to need intravenous iron.

Beyond addressing the immediate medical and psychosocial needs of these women, there is the issue of pedigree. Often the delayed health-seeking behavior is due to a familial phenotype (Powers et al, 2018). If related family members also miss school or work due to HMB, then an acceptance of this pattern as being perceived as normal is likely. The big picture goal in identifying and characterizing this inception cohort is to raise awareness of the frequency of HMB presentation in hospital emergency departments. With this quantification of the HMB burden, public health may be able to consider how to reduce the population burden. Moving forward, precision medicine approaches become more commonly integrated into public health and health care delivery systems (Ramaswami et al., 2018). Identifying bleeding disorders such as von Willebrand disease or platelet dysfunctions should be considered when bleeding history is suggestive. Women with HMB should not be simply discharged from the ED with potentially very few therapeutic options such as hormonal therapy or oral contraceptives. Identifying family linkages and ensuring that a history of unattended excessive bleeding is not considered normal reproductive health and consequently ignored by healthcare providers is one long-term goal of this project.

Conclusions

Analysis of an inception cohort of 111,555 women who presented to the emergency department with heavy menstrual bleeding symptoms revealed a prevalence of women from low median income households who were more likely to be hospitalized as they aged. For these women who are theorized to delay health-seeking behavior, those in the smallest population locations were at greatest risk for hospitalization. This project did not attempt to assign causality but did estimate associated risk using the health determinants available from the HCUP databases accessed. The findings reported a need to be examined prospectively to confirm the role of location, economic status, and explore the contribution of racial background, educational attainment, and more robust health surrogates such as body mass index.

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Appendix A: SPSS Programing Code for Data Extraction

SPSS Code for Whole Heavy Menstrual Bleeding Cohort from NEDS Database

```
GET
  FILE='C:\Users\Henry\Documents\PhD\PhD Project\HCUP Database\NEDS
2016\NEDS_2016 (2)\NEDS 2016 HMB Data Set\NEDS Data 2016 HMB Core Data
SET Feb20.sav'.
DATASET NAME DataSet1 WINDOW=FRONT.
USE ALL.
COMPUTE filter_$=((I10_DX1 = "N920" OR I10_DX1 = "N921" OR I10_DX1 =
"N922" OR I10_DX1 = "N923" OR
    I10_DX1 = "N924" OR I10_DX1 = "N925" OR I10_DX1 = "N926" OR I10_DX1
= "N930" OR I10_DX1 = "N938" OR
    I10_DX1 = "N939") AND (AGE >= 10 AND AGE <= 60)).
VARIABLE LABELS filter_$ '(I10_DX1 = "N920" OR I10_DX1 = "N921" OR
I10_DX1 = "N922" OR I10_DX1 = '+
    '"N923" OR I10_DX1 = "N924" OR I10_DX1 = "N925" OR I10_DX1 = "N926"
OR I10_DX1 = "N930" OR '+
    'I10_DX1 = "N938" OR I10_DX1 = "N939") AND (AGE >= 10 AND AGE <=
60) (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
EXAMINE VARIABLES=AGE Pay1
  /PLOT BOXPLOT STEMLEAF HISTOGRAM NPPLOT
  /COMPARE GROUPS
  /STATISTICS DESCRIPTIVES
  /CINTERVAL 95
  /MISSING LISTWISE
  /NOTOTAL.
```

SPSS Code for Logistic Regression Model

```
GET
  FILE='C:\Users\Henry\Documents\PhD\PhD Project\Chapter 4 Results\Logistic Regression
Analysis\Logistic Regression Model File\Core Date Fromated Files\NRD 2016 Core Data HMB
Logit April 20.sav'.
DATASET NAME DataSet1 WINDOW=FRONT.
DATASET ACTIVATE DataSet1.

SAVE OUTFILE='C:\Users\Henry\Documents\PhD\PhD Project\Chapter 4 Results\Logistic
Regression '+
    'Analysis\Logistic Regression Model File\Core Date Fromated Files\NRD 2016 Core Data
HMB Logit '+
    'April 20.sav'
  /COMPRESSED.
GET
  FILE='C:\Users\Henry\Documents\PhD\PhD Project\Chapter 4 Results\Logistic Regression
Analysis\Logistic Regression Model File\Core Date Fromated Files\NEDS 2016 Core Data HMB
Logit April 20.sav'.
DATASET NAME DataSet2 WINDOW=FRONT.
DATASET ACTIVATE DataSet2.

SAVE OUTFILE='C:\Users\Henry\Documents\PhD\PhD Project\Chapter 4 Results\Logistic
Regression '+
    'Analysis\Logistic Regression Model File\Core Date Fromated Files\NEDS 2016 Core Data
HMB '+
    'Logit April 20.sav'
  /COMPRESSED.
DATASET ACTIVATE DataSet1.
DATASET ACTIVATE DataSet1.

SAVE OUTFILE='C:\Users\Henry\Documents\PhD\PhD Project\Chapter 4 Results\Logistic
Regression '+
    'Analysis\Logistic Regression Model File\Core Date Fromated Files\NRD 2016 Core Data
HMB Logit '+
    'April 20.sav'
  /COMPRESSED.
DATASET ACTIVATE DataSet1.

SAVE OUTFILE='C:\Users\Henry\Documents\PhD\PhD Project\Chapter 4 Results\Logistic
Regression '+
    'Analysis\Logistic Regression Model File\Core Date Fromated Files\NRD 2016 Core Data
HMB Logit '+
    'April 20.sav'
  /COMPRESSED.
DATASET ACTIVATE DataSet2.
ADD FILES /FILE=*
  /FILE='DataSet1'.
EXECUTE.
USE ALL.
COMPUTE filter_$=((I10_DX1 = "N939" OR I10_DX1 = "N938" OR I10_DX1 = "N930" OR I10_DX1 =
"N926" OR
    I10_DX1 = "N925" OR I10_DX1 = "N924" OR I10_DX1 = "N923" OR I10_DX1 = "N922" OR
I10_DX1 = "N921" OR
    I10_DX1 = "N920") AND (AGE >= 10 AND AGE <= 60) ).
VARIABLE LABELS filter_$ '(I10_DX1 = "N939" OR I10_DX1 = "N938" OR I10_DX1 = "N930" OR
I10_DX1 = '+
    '"N926" OR I10_DX1 = "N925" OR I10_DX1 = "N924" OR I10_DX1 = "N923" OR I10_DX1 =
"N922" OR '+
    'I10_DX1 = "N921" OR I10_DX1 = "N920") AND (AGE >= 10 AND AGE <= 60)  (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
```

Appendix B: Data Use Agreement

H·CUP
HEALTHCARE COST AND UTILIZATION PROJECT

DATA USE AGREEMENT for the Nationwide Databases from the Healthcare Cost and Utilization Project Agency for Healthcare Research and Quality

This Data Use Agreement ("Agreement") governs the disclosure and use of data in the HCUP Nationwide Databases from the Healthcare Cost and Utilization Project (HCUP) which are maintained by the Center for Delivery, Organization, and Markets (CDOM) within the Agency for Healthcare Research and Quality (AHRQ). The HCUP Nationwide databases include the National (Nationwide) Inpatient Sample (NIS), Kids' Inpatient Database (KID), Nationwide Emergency Department Sample (NEDS), and Nationwide Readmissions Database (NRD). Any person ("the data recipient") seeking permission from AHRQ to access HCUP Nationwide Databases must sign and submit this Agreement to AHRQ or its agent, and complete the online Data Use Agreement Training Course at www.hcup-us.ahrq.gov, as a precondition to the granting of such permission.

Section 944(c) of the Public Health Service Act (42 U.S.C. 299c-3(c)) ("the AHRQ Confidentiality Statute"), requires that data collected by AHRQ that identify individuals or establishments be used only for the purpose for which they were supplied. Pursuant to this Agreement, data released to AHRQ for the HCUP Databases are subject to the data standards and protections established by the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (P.L. 104-191) and implementing regulations ("the Privacy Rule"). Accordingly, HCUP Databases may only be released in "limited data set" form, as that term is defined by the Privacy Rule, 45 C.F.R. § 164.514(e). HCUP data may only be used by the data recipient for research which may include analysis and aggregate statistical reporting. AHRQ classifies HCUP data as protected health information under the HIPAA Privacy Rule, 45 C.F.R. § 160.103. By executing this Agreement, the data recipient understands and affirms that HCUP data may only be used for the prescribed purposes, and consistent with the following standards:

No Identification of Persons–The AHRQ Confidentiality Statute prohibits the use of HCUP data to identify any person (including but not limited to patients, physicians, and other health care providers). The use of HCUP Databases to identify any person constitutes a violation of this Agreement and may constitute a violation of the AHRQ Confidentiality Statute and the HIPAA Privacy Rule. This Agreement prohibits data recipients from releasing, disclosing, publishing, or presenting any individually identifying information obtained under its terms. AHRQ omits from the data set all direct identifiers that are required to be excluded from limited data sets as consistent with the HIPAA Privacy Rule. AHRQ and the data recipient(s) acknowledge that it may be possible for a data recipient, through deliberate technical analysis of the data sets and with outside information, to attempt to ascertain the identity of particular persons. Risk of individual identification of persons is increased when observations (i.e., individual discharge records) in any given cell of tabulated data is ≤10. This Agreement expressly prohibits any attempt to identify individuals, including by the use of vulnerability analysis or penetration testing. In addition, methods that could be used to identify individuals directly or indirectly shall not be disclosed, released, or published. Data recipients shall not attempt to contact individuals for any purpose whatsoever, including verifying information supplied in the data set. Any questions about the data must be referred exclusively to AHRQ. By executing this Agreement, the data recipient understands and agrees that actual and considerable harm will ensue if he or she attempts to identify individuals. The data recipient also understands and agrees that actual and considerable harm will ensue if he or she intentionally or negligently discloses, releases, or publishes information that identifies individuals or can be used to identify individuals.

Use of Establishment Identifiers–The AHRQ Confidentiality Statute prohibits the use of HCUP data to identify establishments unless the individual establishment has consented. Permission is obtained from the HCUP data sources (i.e., state data organizations, hospital associations, and data consortia) to use the identification of hospital establishments (when such identification appears in the data sets) for research, analysis, and aggregate statistical reporting. This may include linking institutional information from outside data sets for these purposes. Such purpose does *not* include the use of information in the data sets concerning individual establishments for commercial or competitive purposes involving those individual establishments, or to determine the rights, benefits, or privileges of establishments. Data recipients are prohibited from identifying establishments directly or by inference in disseminated material. In addition, users of the data are prohibited from contacting establishments for the purpose of verifying information supplied in the data set. Any questions about the data must be referred exclusively to AHRQ. Misuse of identifiable HCUP data about hospitals or any other establishment constitutes a violation of this Agreement and may constitute a violation of the AHRQ Confidentiality Statute.

The undersigned data recipients provide the following affirmations concerning HCUP data:

Protection of Individuals

- I will not release or disclose, and will take all necessary and reasonable precautions to prohibit others from releasing or disclosing, any information that directly or indirectly identifies persons. This includes attempts to identify individuals through the use of vulnerability analysis or penetration testing.

- I acknowledge that the release or disclosure of information where the number of observations (i.e., individual discharge records) in any given cell of tabulated data is ≤10 can increase the risk for identification of persons. I will consider this risk and avoid publication of a cell containing a value of 1 to 10.

- I will not attempt to link, and will prohibit others from attempting to link, the discharge records of persons in the data set with individually identifiable records from any other source.

- I will not attempt to use and will take all necessary and reasonable precautions to prohibit others from using the data set to contact any persons in the data for any purpose.

Protection of Establishments

- I will not publish or report, through any medium, data that could identify individual establishments directly or by inference.

- When the identities of establishments are not provided in the data sets, I will not attempt to use and will take all necessary and reasonable precautions to prohibit others from using the data set to learn the identity of any establishment.

- I will not use and will take all necessary and reasonable precautions to prohibit others from using the data set concerning individual establishments: (1) for commercial or competitive purposes involving those individual establishments; or (2) to determine the rights, benefits, or privileges of individual establishments.

- I will not contact and will take all necessary and reasonable precautions to prohibit others from contacting establishments identified in the data set to question, verify, or discuss data in the HCUP databases.

- I acknowledge that the HCUP NIS, KID, and NRD may contain data elements from proprietary restricted computer software (e.g., 3M™ APR DRGs) supplied by private vendors to AHRQ for the sole purpose of supporting research and analysis with the HCUP NIS, KID, and NRD. While I may freely use these data elements in my research work using the HCUP NIS, KID, and NRD I agree that I will not use and will prohibit others from using these proprietary data elements for any commercial purpose. In addition, I will enter into a separate agreement with the appropriate organization or firm for the right to use such proprietary data elements for commercial purposes. In particular, I agree not to disassemble, decompile, or otherwise reverse-engineer the proprietary software, and I will prohibit others from doing so.

Limitations on the Disclosure of Data and Safeguards

- I acknowledge and affirm that I am personally responsible for compliance with the terms of this Agreement, to the exclusion of any other party, regardless of such party's role in sponsoring or funding the research that is the subject of this Agreement.

- I will only allow access to HCUP Nationwide data to those who have become authorized users of the HCUP data by signing a copy of this Data Use Agreement and completing the online Data Use Agreement Training Course at www.hcup-us.ahrq.gov. Before granting any individual access to the data set, I will submit the signed data use agreements to the address at the end of this Agreement.

- I will not use or disclose and I will prohibit others from using or disclosing the data set, or any part thereof, except for research, analysis, and aggregate statistical reporting, and only as permitted by this Agreement.

- I will not redistribute HCUP data by posting on any Website or other publicly-accessible online repository.

- I will ensure that the data are kept in a secured environment and that only authorized users will have access to the data.

- I acknowledge and affirm that interpretations, conclusions, and/or opinions that I reach as a result of my analyses of the data sets are my interpretations, conclusions, and/or opinions, and do not constitute the findings, policies, or recommendations of the U.S. Government, the U.S. Department of Health and Human Services, or AHRQ.

- I agree to acknowledge in all reports based on these data that the source of the data is the "National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality." Substitute "Nationwide Inpatient Sample (NIS)" (if using data prior to 2012), "Kids' Inpatient Database (KID)," "Nationwide Emergency Department Sample (NEDS)," or "Nationwide Readmissions Database (NRD)" as appropriate.

- I will indemnify, defend, and hold harmless AHRQ and the data organizations that provide data to AHRQ for HCUP from any or all claims and losses accruing to any person, organizations, or other legal entity as a result of violation of this Agreement. This provision applies only to the extent permitted by Federal and State law.

- I agree to report the violation or apparent violation of any term of this Agreement to AHRQ without unreasonable delay and in no case later than 30 calendar days of becoming aware of the violation or apparent violation.

Terms, Breach, and Compliance

Any violation of the terms of this Agreement shall be grounds for immediate termination of this Agreement. AHRQ shall determine whether a data recipient has violated any term of the Agreement. AHRQ shall determine what actions, if any, are necessary to remedy a violation of this Agreement, and the data recipient(s) shall comply with pertinent instructions from AHRQ. Actions taken by AHRQ may include but not be limited to providing notice of the termination or violation to affected parties and prohibiting data recipient(s) from accessing HCUP data in the future.

In the event AHRQ terminates this Agreement due to a violation, or finds the data recipient(s) to be in violation of this Agreement, AHRQ may direct that the undersigned data recipient(s) immediately return all copies of the HCUP Nationwide Databases to AHRQ or its designee without refund of purchase fees.

Acknowledgment

I understand that this Agreement is requested by the United States Agency for Healthcare Research and Quality to ensure compliance with the AHRQ Confidentiality Statute. My signature indicates that I understand the terms of this Agreement and that I agree to comply with its terms. I understand that a violation of the AHRQ Confidentiality Statute may be subject to a civil penalty of up to $14,140 under 42 U.S.C. 299c-3(d), and that deliberately making a false statement about this or any matter within the jurisdiction of any department or agency of the Federal Government violates 18 U.S.C. § 1001 and is punishable by a fine, up to five years in prison, or both. Violators of this Agreement may also be subject to penalties under state confidentiality statutes that apply to these data for particular states.

Signed: ______ Date: Oct 23/18

Print or Type Name: HENRY MEAD

Title: PhD candidate

Organization: Walden University

Address: [redacted]

Address: ______

City: [redacted] State: [redacted] ZIP Code: [redacted]

Phone: [redacted] Fax: ______

E-mail: henry.mead@waldenu.edu

The information above is maintained by AHRQ only for the purpose of enforcement of this Agreement and for notification in the event data errors occur.

Note to Purchaser: Shipment of the requested data product will only be made to the person who signs this Agreement, unless special arrangements that safeguard the data are made with AHRQ or its agent.

Submission Information

Please send signed HCUP Data Use Agreements and proof of online training to:

HCUP Central Distributor
Social & Scientific Systems, Inc.
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910
E-mail: HCUPDistributor@AHRQ.gov
Fax: (866) 792-5313

According to the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number. The valid OMB control number for this information collection is 0935-0206. The time required to complete this information collection is estimated to average 30 minutes per response, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection. If you have any comments concerning the accuracy of the time estimate(s) or suggestions for improving this form, please write to: Agency for Healthcare Research and Quality, Attn: Reports Clearance Officer, 5600 Fishers Lane, Rockville, Maryland 20857.

OMB Control No. 0935-0206 expires 01/31/2019.

CERTIFICATE OF COMPLETION

Awarded To

Henry Mead

For Successfully Completing

HCUP DATA USE AGREEMENT TRAINING

On

10/23/2018

YOUR CERTIFICATION CODE IS:

HCUP-379M83CWP

AHRQ

Agency for Healthcare Research and Quality

H·CUP

Statement of Intended Use of HCUP State Databases and Description of Project Activities

A Statement of Intended Use is required if you are requesting SID, SASD, and/or SEDD files from the HCUP Central Distributor. This Statement of Intended Use is reviewed by AHRQ on behalf of the Data Organizations that make their data available through the HCUP Central Distributor ("HCUP Partners").

The Statement of Intended Use should be a brief narrative including enough information for reviewers to assess compliance with the HCUP Data Use Agreement for State Databases and must include:

- A description of the subject area and/or specific project
- The goals and objectives of the project
- The intended audience and anticipated final product(s)
- Any specific reason for requesting the HCUP databases

The DUA provides complete descriptions of the acceptable uses of the HCUP SID, SASD, and SEDD. In general, files from these databases are available for the purposes of research and aggregate statistical reporting. Attempts to identify individuals are strictly prohibited. Information that could identify establishments directly or by inference may not be released in disseminated or shared materials.

Tips for preparing your Statement of Intended Use:

The abstract does not need to be long, but should contain sufficient details so that the reviewer has a fundamental understanding of how the HCUP data will be used and reported. Well-written abstracts are usually about 250 words. Short, terse descriptions often raise questions.

For primarily academic purchasers, this abstract is similar to one that would be submitted for possible presentation at an academic conference where the data analysis has not been completed.

For primarily non-academic purchasers, some features of the intended use that help reviewers understand the project better include:

- What are the levels of aggregated statistics being investigated (e.g., geographic, hospital, condition-specific)?
- What are the expected products (e.g., client reports, tables, peer-review manuscripts)?
- Who are the main audiences (e.g., academic, clients)? If "clients", who are your clients?
- How will the audience use this information?

Notes:

1. Exploratory use is permissible, but should be clearly stated in the Statement of Intended Use submitted with your order. Further, as concrete projects emerge from approved exploratory work, the data custodian must submit a "Re-use Request" to the HCUP Central Distributor for review and approval by AHRQ before work may begin on any new, specific project.
2. Even if you are purchasing additional data for a previously approved project, you must provide the complete project description for each individual purchase. Failure to do so will delay the review of the new application(s). If you have the order number(s) for the related purchases available, please also include them.
3. ***The AHRQ reviewers will put your application on hold and request additional clarification from you if you do not provide all of the information requested.***

Responsibilities of the Data Purchaser

All users of HCUP data must agree to the terms of the HCUP Data Use Agreement. Being the data purchaser carries additional responsibilities to which you must agree.

In order to facilitate your data request, please confirm your understanding of the following:

1. Data Custodian: Unless otherwise designated and agreed upon by AHRQ, the data purchaser is considered the "data custodian" of HCUP data. The data custodian is responsible for ensuring that the HCUP data are kept secured, that only authorized users have access to the data, and that HCUP data are used in a way that is consistent with the Data Use Agreement.

2. Data Access by Others: The data custodian is responsible for obtaining proof of Data Use Agreement (DUA) training and signed HCUP DUAs from anyone who has access to the data or output that contains small cell sizes, individual records, or identifies hospitals. Training completion certificates and DUAs must be sent to the HCUP Central Distributor before access is granted to these individuals.

The data custodian is held accountable for the proper use of the HCUP data that they have purchased, even by other individuals to whom they have given access. As a result, the data custodian is also responsible for any possible misuse of the data (unintended or otherwise) along with the data user.

3. Statement of Intended Use: A "Statement of Intended Use" is required for all requests for State Databases (i.e., SID, SASD, SEDD). The "Statement of Intended Use" submitted with your order must include enough information for AHRQ to understand the subject area of interest, how the data will be used, intended audiences, and anticipated end-products (e.g., tables and charts, internal reports, peer-review journal articles). Exploratory use is permissible, but this should be made clear in the "Statement of Intended Use."

4. New Projects: Each application and approval for State-level data is project-specific. If the data (i.e., SID, SASD, SEDD) will be used for a purpose other than that originally approved, or as concrete projects emerge from approved exploratory work, the data custodian must submit a "Re-use Request" to the HCUP Central Distributor for review and approval by AHRQ before work may begin on the new project. (This form may be found at www.hcup-us.ahrq.gov/tech_assist/centdist.jsp.)

Signed: Hay Mead Date: Oct 23/18

By signing this document, I acknowledge I have read, understand, and will comply with the Responsibilities of the Data Purchaser.