Obesity, Cardiometabolic Disease, and Postoperative Acute Kidney Injury: A Retrospective Cohort Study

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Epidemiological Science)
in The University of Michigan
2022

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Dedication

To my grandfather J. Clark Leis (Pap-Pap), whose tenacity and stubbornness I inherited and without which this dissertation would not have been possible.

"The most important step a person can take is the next one. Always the next step."

~Brandon Sanderson, Oathbringer

Acknowledgements

I have so many people to thank for helping me through this process, more than could ever fit on a few pages. First, to all of those in the Epidemiology department, especially those in the Center for Midlife Science and the Martin/Monto lab for so warmly welcoming me into your research groups, and teaching me so much about how to be a better researcher. From refining my research question to how to write a relatively coherent first draft of an introduction or discussion, and even EndNote – I have learned so much from you all. I'd also like to thank Nancy Francis, who took the time to meet with me and answer all my many, many, many questions before I applied to the program.

From the Anesthesia department, I'd like to thank all of the anesthesiologists I've worked with in my time here, especially those in the Head and Neck and Pediatrics groups, who were so enthusiastic in teaching me the "why" behind the research we were doing and answering all of my clinical questions about why things worked the way they did. What you taught me directly led to this dissertation. I'd also like to thank Ron Frazier, Mikele Garrett, Justin Ortwine, and Baorong Shi, who collectively spent a few hundred hours over the years explaining the intricacies of the underlying data structures of our electronic health record systems, helping me learn how best to use them for research, and answering my many questions along the way. This information formed the backbone of my dissertation and significantly contributed to the success of my analyses – thank you all for taking the time to teach a curious statistician!

A big thank you to all of my family and friends who have supported me through this process! To my father and sister for always encouraging me to ask questions (and usually

answering them). To my band friends from the Washtenaw Community Concert Band, for making Tuesday nights always entertaining, and especially to Amy Sierzega, Sara-Marie Kuntz, and Emily Gauld for your continued friendship and support, and exemplifying what it means to be extraordinarily strong, bad-ass women achieving great things and making a difference in the world.

To my Michigan family Justin Ortwine, Jess Espenshade, and Tomas Medina, you all were some of my first friends here in Michigan and have been there for me and supported me since the beginning. Thank you for all of the board game days, lunches, witty banter, and companionship through this process and the pandemic! I am greatly looking forward to many stress- and guilt-free board game days and adventures post-defense! Your friendship through the years has provided so much light in my life, and I am so, so thankful for you all.

A special shoutout to all of the pets who helped in the making of this dissertation, especially my boys Pockets and Goose, and my friends' pets (Banana, Moose, Xander, Echo, Java, Basil, Maggie, Nash, Posie, and Fiona) for providing lots of snuggles as I worked through the doctoral experience and keeping me company during the long days of the pandemic!

I would also like to thank and acknowledge the many mentors who have helped me get here. First my committee, for your support and guidance through this process. I have learned so much from you. Thank you for taking the time to walk me through the intricacies of your respective fields, and being so patient with me while I learned, especially Matt and Jen who guided me through my first major analysis using genetic data and Mike for your continued clinical guidance and enthusiasm for my research questions. To Dr. Hill, my advisor from Bonas - I have never met someone with as much enthusiasm for calculus and joy in celebrating math holidays like pi day and integral day as you. Thank you for always encouraging me to embrace

what I loved and supporting me through all of that, even when it resulted in two major changes and an insane credit load for 3 years. To Jesse Chittams, my internship mentor from Penn - I would not have ended up at U of M and in this program if you hadn't given me a chance as a stats intern with absolutely no experience but a lot of motivation. I use the analytic skills I learned from you every day and have even carried forward your folder organization structure to all of my projects, including this dissertation.

And finally, to Carrie. From even before I was accepted into this program you were so enthusiastic about my ideas for this dissertation and for my career. You have given me so many opportunities to grow and to learn and to thrive, and I wouldn't have gotten here without your steadfast support and guidance through this doctoral process and all of the major life events that wormed their way into the last 4 years. You inspire me to be a better researcher each day, and I hope to approach my future roles with as much passion and love as you have for your work. I will never be able to fully thank you for everything you've done for me, but I hope to be able to pay it forward some day!

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List of Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
AKI	Acute Kidney Injury
BMI	Body Mass Index
CAD	Coronary Artery Disease
CHF	Congestive Heart Failure
CVD	Cardiovascular Disease
eGFR	Estimated Glomerular Filtration Rate
EHR	Electronic Health Record
GWAS	Genome-Wide Association Study
HbA1c	Hemoglobin A1C
HTN	Hypertension
ICD	International Classification of Disease
MAP	Mean Arterial Pressure
MetS	Metabolic Syndrome
mMetS	Modified Metabolic Syndrome
MGI	Michigan Genomics Initiative
MHO	Metabolically healthy obesity
MPOG	Multicenter Perioperative Outcomes Group
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OR	Odds Ratio
pRBC	Packed Red Blood Cell (blood transfusion)
PRS	Polygenic Risk Score
WHO	World Health Organization
95% CI	95% Confidence Interval

Note: *Type 2 diabetes mellitus* and *diabetes* are used interchangeably within this dissertation.

Abstract

The burden of obesity and cardiometabolic conditions increases in prevalence with age. Thus, more complex medical care is needed to manage these conditions and their possible resulting effects, including surgical procedures and management of potential adverse postoperative outcomes. This dissertation examines the association between obesity, cardiometabolic disease, and postoperative acute kidney injury (AKI). To address the aims, we utilize data from a) a multicenter cohort of patients with total knee and hip replacements, and b) a single-center cohort of surgical patients enhanced with genetic data.

In Chapter 2 (Aim 1), we evaluated latent classes of cardiometabolic conditions among patients in a multicenter cohort of total joint arthroplasty cases and found three robust groups: (1) a class with moderate probability of hypertension and low probability of other factors representing 45.2% (n = 37,032) of the population; (2) a class with high probability of hypertension and high cholesterol and moderate probability of diabetes representing 45.1% (n=36,889) of the population; and (3) a class with high probability of hypertension, high cholesterol, cardiac arrhythmias, coronary artery disease (CAD), and congestive heart failure (CHF), and moderate probability of diabetes and peripheral vascular disease representing 9.7% (n=7,950) of the population. Obesity and cardiovascular disease were associated with increased risk of AKI within 7 days following surgery. Compared to those in class 1 without obesity, those in class 3 with obesity had 3.6 times the odds of AKI (95%CI:3.1,4.3) while those in class 3 without obesity had 2.5 times the odds of AKI (95%CI:2.0,3.0) compared to the same group.

Individuals with more significant cardiometabolic disease had higher odds of AKI regardless of the presence of obesity, though obesity conferred additional risk.

In Chapter 3 (Aim 2), we examined whether the associations between cardiometabolic class, obesity, and AKI were mediated by modifiable intraoperative factors of general anesthesia use and minutes of intraoperative hypotension. There was little evidence of a clinically significant mediating effect of general anesthesia use or minutes of hypotension. Thus, while these factors are independent risk factors for acute kidney injury, controlling these factors intraoperatively appears to not meaningfully reduce the risk of AKI conferred by cardiometabolic comorbidity.

In Chapter 4 (Aim 3), we utilized validated and published polygenic risk scores (PRS) for type 2 diabetes, coronary artery disease, and BMI in a single-center cohort of surgical patients to assess the association between these PRS and postoperative AKI. There was little evidence of an association between PRS and AKI both overall and after adjustment. Notably, however, we found that the PRS performed similarly to the disease phenotype when assessing overall model discrimination, indicating the potential utility of these scores in datasets where robust electronic health record data for these complex conditions are not available, or where the phenotype may not yet have occurred.

This dissertation evaluates the effect of phenotypic and polygenic risk of cardiometabolic conditions and obesity on the development of postoperative acute kidney injury. The results suggest that the differential risk conferred by patterning of cardiometabolic disease requires additional clinician consideration when determining the best course of postoperative care, specifically around monitoring for AKI. More research is needed to determine what mechanistic

factors, such as systemic inflammation, may be driving the observed associations to more fully inform who is most at risk for AKI following surgeries.

Chapter 1

Introduction

1.1. Background

According to the 2015-2016 National Health and Nutrition Examination Survey (NHANES) data reported by the Centers for Disease Control and Prevention (CDC), the age-adjusted rates of cardiometabolic diseases such as diabetes, high cholesterol, hypertension, and obesity in the United States range from 12.2% - 71.3% with high total cholesterol having the lowest rate and obesity the highest[1]. Currently, individuals over age 65 represent 16% of the population, and that number is expected to reach 25% by 2060[2]. The burgeoning population of older adults suggests that the burden of cardiometabolic disease may substantially increase in the coming years given that the prevalence of these conditions increase with age. Based on data from NHANES 2013-2016, only 4.2% of those aged 18-44 years had diabetes, compared to 17.5% of those aged 45-64 years and 26.8% of those aged ≥ 65.[3] Similar trends exist for hypertension[4]. The national prevalence of obesity is currently 40%, and is expected to increase to approximately 50% nationwide by 2030[5].

With a rise in population age and the increasing presence of comorbidities comes a trend toward more complex medical care needed to manage these conditions and their resulting effects. In particular, recent findings suggest an increase in surgical procedures over time, and higher rates of surgery among older adults. Among adults in England, the pooled mean age of surgical patients increased from 47.5 years in 1999 to 54.2 years in 2015[6], highlighting that the surgical population as a whole is aging. Additionally, holding age constant the number of patients >60

years of age receiving surgery increased from 36.1% to 47.6% in the same time frame[6]. A similar trend would be expected within the United States, though this data is not readily available. It is important to note that the rate of many postoperative outcomes increases with age, including stroke[7] and AKI[8].

No surgical procedure, however common, comes without risk. In addition to preoperative factors elevating an individual's risk of adverse events during the postoperative period, there are additional risks of intraoperative adverse events. These intraoperative events, such as sustained low blood pressure, can also impact an individual's propensity to develop postoperative events. A 2016 international prospective study of elective inpatient procedures showed that approximately 20% of patients in high-income countries experienced a post-operative complication within 7 days of the procedure, with an overall mortality rate of 0.5%[9]. Post-operative complications are not only associated with morbidity and mortality[10], but also associated with substantial additional economic costs. In-patient hospital costs are at least twice as high for procedures followed by a complication compared to those without[11]. Following the acute (short-term) complication episode, some of the most severe complications such as stroke, myocardial infarction, and acute kidney injury (AKI) can have lasting effects on the patients including an increase in mortality more than a month after surgery[12].

Cardiometabolic comorbidities such as cardiovascular disease and obesity are known risk factors for many postoperative complications[13-15], though questions remain regarding the mechanism of action, specifically whether it is the condition itself or potential downstream systemic effects such as increased inflammation[16]. Despite the fundamental nature of this question, there is a dearth of information regarding the joint effects of these conditions. A 2010 study by Glance et al examined the occurrence of postoperative AKI in non-cardiac surgery

patients with modified metabolic symptom (mMetS), defined as having all of obesity, diabetes, and hypertension[13]. After adjusting for age, sex, surgical complexity, admission source, functional status, wound classification, preoperative hematocrit, and comorbidities, those who were obese without mMetS had 1.6 times the odds (95% CI: 1.4, 1.9) of developing AKI compared to those who were normal weight without mMetS, and those who were obese with mMetS had 3.3 times the odds (95% CI: 2.8, 3.9) of developing AKI compared to those who were normal weight without mMetS. For both obese with and without mMetS, there was a significant increase in the odds ratio for body mass index (BMI) category reflecting higher levels of obesity. Similar results were seen for cardiac, pulmonary, and central nervous system outcomes. Although obesity in the absence of other comorbidities was associated with a modest increase in the odds of perioperative complications, there was a significant additional increase in odds of these events when obesity was comorbid with other conditions. Glance et al. showed this difference to be most pronounced in the outcome of AKI, where compared to those normal weight without mMetS the odds increased from 2.0 (95% CI: 1.6, 2.5) for those with morbid obesity alone to 5.0 (95% CI: 3.9, 6.5) when the morbid obesity was coupled with hypertension and diabetes; similarly, the odds increased from 3.1 to 7.3 for super obese without and with the presence of mMetS, respectively[13].

A number of single- and multi-center studies of both cardiac and general non-cardiac surgical populations have shown pre-existing comorbidities such as hypertension, diabetes, and high body mass index to be independent predictors of postoperative AKI[8,17-22]. However, no studies to date have examined how differential joint presentations of these conditions with or without obesity affects risk of outcomes such as AKI. This is especially important given that these conditions often do not exist in isolation. Approximately 34% of all adults have metabolic

syndrome, defined as having at least three of the following: elevated glucose, low high-density lipoprotein, elevated triglycerides, large waist circumference, and hypertension[23] yet there is substantial heterogeneity in the patterning of which features qualify someone as meeting this criteria[24].

Despite the known co-occurrence of obesity with diseases such as diabetes and hypertension, there remain a number of obese individuals who are otherwise healthy without additional cardiometabolic conditions – a condition known as "metabolically healthy obese" (MHO)[25]. There are a number of different definitions for metabolic health, with most consisting of some combination of obesity (or waist circumference), hypertension, diabetes, and hyperlipidemia[26]. The prevalence of this healthy obesity phenotype varies widely[25]; a study examining varied MHO definitions showed a prevalence in men from 3% to 32%, and in women from 11% to 43%[27]. In a study by Glance et al., among more than 110,000 patients with obesity, only 17.5% met the criteria for mMetS (meaning had both diabetes and hypertension) while 82.5% did not[13]. Metabolically healthy obese individuals have been shown to have higher insulin sensitivity and cardiovascular fitness than those who are metabolically unhealthy obese[25]. However, the concept of metabolically healthy obesity is contentious within the medical community, in part due to lack of a standardized definition, thereby resulting in inconsistent research[28]. For example, estimates of MHO prevalence, timing, and clinical sequelae vary widely, thereby calling into question the validity of the condition itself. The prevalence of MHO decreases with age, and there exists controversy over whether the state is persistent or transient if preventative lifestyle factors are not maintained[29]. A recent study found this transition from MHO to metabolically unhealthy obesity occurred at a rate of 44% over 10 years, with higher BMI and a longer duration of obesity contributing to this transition[30]. However, 26% of those

who were not obese at baseline also transitioned to a metabolically unhealthy state during this time, suggesting that obesity is not the only contributing factor to developing poor metabolic health, though those with obesity appear to develop these cardiometabolic comorbidities at a higher rate[30]. Together, this body of research suggests that while obesity is a contributing factor to further cardiometabolic disease, having a high weight alone is not the sole contributing factor; lifestyle factors such as low socioeconomic status, mental health issues, and lack of exercise may also contribute to the development of additional cardiometabolic disease[31].

For example, increasing physical activity has been shown to improve cardiovascular fitness and reduce the risk of conditions such as type 2 diabetes and hypertension even in obese individuals[32,33]. However, those who are obese are more likely to suffer from mobility limitations. Obesity is a known risk factor for osteoarthritis, and that risk increases with the presence of additional cardiometabolic diseases such as diabetes[34]. There is concern that with the escalating frequency of morbid obesity that we may be in the midst of an arthritis epidemic[34]. Osteoarthritis is a common indication for elective knee and hip replacement procedures, which are performed over 5 years earlier, on average, in obese patients than those of normal weight[35,36]. This may be due to the implementation of guidelines from the American Association of Hip and Knee Surgeons which recommend caution in performing arthroplasty procedures on individuals with a BMI $\geq$ 30kg/m^2 and delaying care in those with a BMI $\geq$40 kg/m^2 due to the increased risk of complication[37]. Some institutions carry policies for a maximum eligible BMI for total joint arthroplasty[38,39] and surgeons may set their own BMI thresholds[40] resulting in the patient being refused surgery until they can lose weight. However, post-total-joint-arthroplasty functional gains in obese individuals are equivalent to or greater than those of normal weight[41-43], thereby highlighting the important value of this surgery in patients with obesity. Further, while

the guidelines state that comorbidities such as uncontrolled diabetes should be taken into account in surgical decision making, this is often not the case when strict guidelines based solely on BMI are implemented[37]. Of course, these procedures are not without risk; however, estimates suggest that restricting BMI to ≤35 kg/m^2 would deny 16 patients a complication-free surgery for every one patient with a complication, and a cutoff of ≤45 kg/m^2 would deny 10 patients a complication-free surgery[44]. Given the increased prevalence of obesity, there therefore exists a significant number of individuals being denied complication-free, life changing surgery. Thus, more information is needed to identify patients truly at greatest risk for adverse surgical outcomes, including characterization of their obesity and overall health status.

1.2. Physiological Mechanisms of Diseases

Obesity

Obesity is defined by the World Health Organization (WHO) as a BMI ≥ 30 kg/m^2, and can be further categorized into class 1 obesity (30 – 34.9kg/m^2), class 2 obesity (35 – 39.9kg/m^2) and class 3 obesity (≥40 kg/m^2)[45]. Obesity manifests physically as an excess of adipose tissue, though the distribution of this tissue varies[25]; adipose tissue itself is found throughout the body, including under the skin, within and around organs, and in bone marrow[46]. In addition to energy storage, research in the early 2000s showed adipose tissue to be a major producer of endocrine hormones and cytokines, including both pro- and anti-inflammatory products[47], as shown in Figure 1.1[47]. These products are often highly metabolically active; for example, leptin is directly related to insulin secretion, and there is some evidence to suggest higher levels of leptin may be associated with development of type 2 diabetes[48]. Additionally, many of the hormones produced by adipose tissue are related to additional adipose tissue accumulation, blood pressure regulation, insulin regulation, lipid metabolism, and general inflammation[23].

However, not all adipose tissue is the same. All humans have some level of subcutaneous fat, which is stored just under the skin and is the body's natural energy stores from excess energy intake[49]. When too much fat is produced than can be stored as subcutaneous tissue, it begins to accumulate as visceral adipose tissue within the abdominal cavity around internal organs[49]. Visceral and subcutaneous adipose tissues are vastly different in structure and hormone secretion. Indeed, visceral adipose tissue is more vascular, and produces higher quantities of pro-insulin-resistance and pro-inflammatory adipocytes[49]. Studies have shown that increased visceral fat accumulation is an independent risk factor for diabetes[50], hypertriglyceridemia and high cholesterol[51], hypertension[52,53], and cardiovascular disease[54]. To accommodate the highly vascular nature of this visceral adipose tissue, severe obesity is accompanied by an increase in total blood volume and, in conjunction, an increase in cardiac output. This increases stress on the ventricles of the heart and blood vessels throughout the body[55]. Conversely, increased amounts of subcutaneous fat have not been associated with increased risk of cardiometabolic disease [56]. It is important to note that BMI does not specify the location of adipose tissue, measure changes in distribution over time, or differentiate between adipose tissue levels in men and women; together, this makes BMI a less-reliable indicator of future cardiovascular risk than measures of adipose tissue[57-59].

Diabetes

Type 2 diabetes mellitus is a state of hyperglycemia characterized as a fasting blood glucose ≥ 126 mg/dl or hemoglobin A1C (HbA1c), a measure of the average blood glucose over the prior 2-3 months, ≥ 6.5%[60]. Briefly, following food consumption, the higher concentration of sugar within the bloodstream promotes insulin secretion by the pancreas[61]. Insulin itself stimulates both the uptake of glucose into tissue cells for immediate energy use, as well as storage for later use within the liver; as the amount of sugar in the blood decreases, the pancreas

releases less insulin. However, over time insulin-sensitive tissues can become less responsive to glucose uptake from insulin signaling, a condition called insulin resistance[61]. Insulin resistance results in an increase in blood glucose, usually in conjunction with a decrease in insulin production from β cells in the pancreas which are responsible for controlling glucose later released by the liver[62]. In combination this results in a decrease of muscular glucose uptake with an increase in glucose production from the liver.

The development of type 2 diabetes is complex, with an individual's propensity to develop the disease influenced by many factors. Lifestyle factors associated with the risk of diabetes include poor diet quality, sedentary lifestyle, and low socioeconomic status[62,63] (Figure 1.2). Additionally, there is a strong genetic risk of diabetes[64]. Although genome-wide association studies have found over 100 possible single nucleotide polymorphisms (SNPs) associated with diabetes, most related loci have small effect sizes and the mechanisms associated with many of these SNPs in the pathophysiology of diabetes remains largely unknown[65]. Stronger associations have been observed in loci related to the adipocytokine-signal pathway[66] and liver and pancreatic cell development[67]. Though no organ system is spared the systemic inflammatory effects of diabetes, the vascular effects of this disease are among the most detrimental and can lead to atherosclerosis, retinopathy, and nephropathy[68,69]. Therefore, the initial prevention of diabetes is of significant public health concern.

Hypertension

Chronic hypertension is a state of prolonged elevated blood pressure, and is characterized based on the systolic or diastolic pressures. The systolic blood pressure represents the pressure inside the vessels during ventricular contraction, when blood is pumped out of the left ventricle of the heart into the aorta. The diastolic pressure is the pressure in the arteries when the ventricles are at rest between contractions[70]. Stage 1 hypertension is defined as a systolic blood

pressure ≥130 mmHg and/or a diastolic blood pressure ≥80 mmHg. Stage 2 hypertension is defined as a systolic pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg[71].

Blood pressure can be regulated through several physiologic systems throughout the body, including vasoconstriction, reduction of cardiac output, and most vitally from the kidney through the renin-angiotensin-aldosterone system (RAAS), which impacts both short-term and long-term blood pressure[72]. When blood pressure decreases the kidney releases the renin enzyme, which splits the hormone angiotensinogen, produced by the liver and regularly circulating in the bloodstream, into angiotensin I and II. Angiotensin II itself constricts arterioles, and additionally signals the release of vasopressin from the pituitary gland to increase blood pressure[73]. When blood pressure is high, the kidneys increase the filtration and excretion of sodium and water waste products to decrease total blood volume[73]. However, dysregulation of the enzymes and hormones within the RAAS, such as from increased inflammation or extra adipose tissue can lead to a consistent state of hypertension[74]. The continued stress on the kidneys in the presence of untreated hypertension can lead to kidney disease and decreased function. Additionally, kidney disease can lead to an increase in blood pressure (secondary hypertension) as the ability of the kidney to assist in the regulation of blood pressure decreases. Prolonged hypertension can lead to coronary artery disease, heart failure, stroke, and death through the development of generalized atherosclerosis, as blood vessels become damaged and less elastic due to a continued high-pressure state and mechanical damage to collagen of the arteries[73].

Diabetes and hypertension share many lifestyle risk factors, including low levels of physical activity and low socioeconomic status[75,76]. Hypertension disproportionately affects African Americans in the United States, and research suggests a stronger impact of

environmental factors such as socioeconomic status rather than genetic factors in this association[77].

1.3. Physiological Mechanisms for Acute Kidney Disease

Kidney Function

When functioning normally, the kidney is a highly vascular organ sitting on either side of the spine that filters about 150 quarts of blood per day – this corresponds to filtering the total blood volume of an average adult (5 L) approximately 28 times per day[78]. Approximately 22% of all cardiac output flows through the kidneys, one of the highest rates in the body[79]. Each kidney is comprised of over a million nephrons (Figure 1.3), which as a whole filter waste products from the blood and return water, glucose, and electrolytes to the bloodstream[80]. The nephron is comprised of a glomerulus and a tubule. The glomerulus consists of a dense and porous bundle of capillaries, which removes waste and fluid from the blood via the glomerular membrane by selective filtering of molecules by factors such as size and electrical charge[81]. After passing through the glomerulus, the filtered product or filtrate from the blood travels to the tubules, where the parallel blood vessels reabsorb the water and electrolytes through a process of countercurrent exchange where the products of the glomerulus flow in the opposite direction of the parallel vessel, creating a countercurrent multiplier system to facilitate movement of molecules by osmotic gradient[82]. The remaining fluid and waste products from the tubule are excreted from the body as urine[80].

Kidneys can lose their functionality, however, as an individual ages or as part of a disease process. A common way to measure kidney function by proxy is through the amount of creatinine present in the bloodstream. Creatinine is a byproduct of skeletal muscle contraction, and is filtered entirely through the kidney with no storage in the body. Thus, a higher blood creatinine level indicates impaired kidney function, because the kidney is unable to filter

creatinine from the blood as well as it should[83]. Normal serum creatinine laboratory values for females range from 0.5-1.1 mg/dL, and from 0.6-1.2 mg/dL for males – the range is slightly higher in males as creatinine is affected by muscle mass[83].

Acute Kidney Injury

Acute kidney injury (AKI) is a major postoperative complication, occurring within 7 days of procedure-triggering event. Although it can occur in other settings, including critical care and as the result of acute physical trauma, this dissertation will focus on AKI in the post-operative setting. Following surgery, AKI is associated with an increased hospital length of stay, higher risk of post-AKI cardiovascular events, and postoperative mortality[14,84,85] (Figure 1.4)[85]. Even those with mild or subclinical AKI following surgery can have lasting health consequences including permanent kidney damage, decreased quality of life, and an increased mortality risk[85].

Postoperative AKI is characterized as a decrease in kidney function after a surgical procedure in relation to preoperative kidney function, as measured by creatinine and urine output[86]. However, despite advances in the field, clinical measures of kidney function remain inadequate to fully capture the diagnosis and thus making it difficult to accurately assess the incidence of this condition[21]. The human body is remarkably adaptable to changes in blood volume such as during surgery, but resilience decreases given pre-existing vascular damage from cardiometabolic comorbidities[21,68,69,73]. Given this, surgery is a vulnerable window for those with comorbidities making them less adaptive to change.

1.4. Known Risk Factors for Acute Kidney Disease

Preoperative factors associated with AKI may damage the kidney's vascular structure over time, making the organ less able to adequately respond to the additional stressors from a surgical procedure. Preoperative obesity may increase the risk of AKI through an increase in inflammatory cytokines and a higher blood volume, thereby providing constant stress on the

organ prior to surgery[84,87]. Although many studies have found diabetes to be associated with AKI, the exact mechanism of action is unknown. It has been hypothesized that the increased risk of AKI associated with diabetes is related to vascular damage from a chronic hyperglycemic state, and in more severe cases of diabetes may also be related to atherosclerosis changes within the kidney which would reduce functionality[88].

Genetic risk associated with AKI has been assessed in both the critical care and intraoperative settings, with most studies examining specific genetic variants rather than genome-wide risk assessment. Such studies have found that insertion/deletion polymorphisms in the *ACE* gene (related to blood pressure regulation[89]) and isoforms of *APO E* (related to metabolism of fats[90]), as well as the T-786C polymorphism in *eNOS* (related to vascular tone[91]), are associated with increased risk of AKI and poor renal function in a surgical populations. However, there have been contradictory findings regarding the role of inflammation-related and other genetic variants in the development of acute kidney injury[92-96], despite the fact that inflammation is hypothesized to be a key mechanism driving the increased risk of AKI among those with obesity and cardiometabolic comorbidities.

In addition to preoperative comorbidities, intraoperative factors such as the use of general anesthesia, use of blood products, and use of nephrotoxic medications are associated with a higher incidence of AKI[84] (Figure 1.5). Intraoperative factors influence the development of AKI through a number of pathways including inflammation, changes to hemodynamics, and nephrotoxicity. Surgery can result in either hypo- or hypervolemia, conditions related to the amount of fluid in the body. Hypovolemia, especially in combination with vasodilators and positive pressure ventilation, can compromise oxygen perfusion and damage organs including the highly vascular kidney. Positive pressure ventilation is used frequently with general

anesthesia, and due to surgical guidelines most non-emergent patients enter the operating room in a mild hypovolemic state, making this combination not infrequent[21].

Hemodynamic changes intraoperatively including prolonged hypotension can cause reduced perfusion to organs and muscular tissue during the procedure[14]. Once this depression is reversed, ischemia-reperfusion occurs and tissues release molecules including High-Mobility-Group-Protein B1 (HMGB1), which is thought to be on the cytokine inflammatory pathway mediated through Toll-like receptor 4[97]. Additional inflammatory factors are released as part of the surgical and healing processes, such as tumor necrosis factor-α and other inflammatory cytokines[98]. This inflammatory response can damage the tubules of the kidney and affect their functionality[21].

1.5. The Role of Precision Medicine in the Prevention of Acute Kidney Injury

Broadly, precision medicine is the use of an individual's unique characteristics such as genetic data or lifestyle factors to determine a tailored course of disease prevention or treatment rather than utilizing a generic approach[99]. Applications of precision medicine vary widely from targeted gene therapies to real-time prediction models[99-101]. The utilization of precision medicine in the intraoperative setting has garnered attention in the last decade with more widespread adoption of electronic health records linked to genetic, biomarker, and wearables data[99]. For a complex condition such as AKI, with numerous potential causes both pre- and intraoperatively, a precision medicine approach may allow for more prompt identification of those at high risk. For example, a real-time risk prediction model integrated within the intraoperative anesthesia management system could identify patients who either entered the operating room at high risk for AKI or who, throughout the procedure, experienced events leading to increased risk and would benefit from a post-operative blood draw to assess kidney function; this would be

especially useful for individuals receiving outpatient surgery in whom AKI may otherwise be missed. This application will be discussed more in-depth in Chapter 5.

There exists a paucity of information regarding the effect of comorbid cardiometabolic disease on risk of postoperative AKI. This above discussion highlights the need for more rigorous examination of the co-occurrence of cardiometabolic disorders, as those with certain co-occurring disease clusters may prove to be at higher risk for postoperative AKI given the complex interplay between diseases such as obesity, diabetes and hypertension with kidney function. This dissertation will more closely examine patterns of cardiometabolic conditions with and without obesity, and the associations between these groups and development of postoperative AKI.

1.6. Specific Aims and Hypotheses

Aim 1: To describe and analyze how cardiometabolic disorder diagnoses cluster together in a multi-center cohort of those presenting for primary total hip or total knee arthroplasty and to examine the association of these clusters with the risk of postoperative acute kidney injury.

Sub Aim #1a. To identify biological and physical latent classes of individuals with diagnosed cardiometabolic conditions including: hypertension, hypotension, hyperlipidemia or hypercholesterolemia, diabetes, peripheral vascular disease, rheumatoid arthritis, hypothyroidism, cardiac arrhythmias, congestive heart failure, coronary artery disease.

Hypothesis. Multiple, distinct classes of individuals will emerge including one generally healthy class of individuals.

Sub Aim #1b. To assess the association between class membership with or without obesity and postoperative acute kidney injury

Hypothesis. Latent classes with symptomology consistent with hypertension and diabetes will have the highest rates of postoperative AKI after adjustment for intraoperative factors, regardless of the presence of obesity.

Aim 2: To determine to what extent the effect of cardiometabolic disorder diagnoses and clustering of these conditions (as determined by Aim 1) on postoperative acute kidney injury is mediated by intraoperative factors known to be associated with AKI in a multi-center cohort of those presenting for primary total hip or total knee arthroplasty.

Sub Aim #2a. To determine the direct and indirect mediating effects of intraoperative factors including hypotension, hypertension, transfusion, total fluid volume, use of general anesthesia, and nephrotoxic medication use on the relationship between latent classes and postoperative AKI.

Hypothesis. There will be a strong mediation effect of these factors on the relationship between latent classes and AKI.

Aim 3: To examine the association between polygenic risk scores (PRS) for comorbidities (type 2 diabetes, coronary artery disease, BMI) and postoperative AKI in a single-center cohort.

Sub Aim 1. To use results from large, replicated GWAS studies to create polygenic risk scores for cardiometabolic diseases in the general surgical population at the University of Michigan utilizing genetic data from the Michigan Genomics Initiative (MGI).

Sub Aim 2. To determine if the PRS defined above are independently associated with risk of AKI after adjusting for other relevant preoperative and intraoperative characteristics, as appropriate

Hypothesis. At least one PRS will be associated with a statistically significant increased odds of AKI after adjustment for other comorbidities.

Sub Aim 3. To determine if inclusion of the PRS improves predictability over a purely clinical model.

Hypothesis. At least one model with PRS will show improvement of the model's predictive capability.

1.7. Conclusion

Given the increased number of surgical procedures being performed in an aging population, and the high burden of comorbid cardiometabolic disease and obesity within this population, there exists an urgent need to more fully understand both who is most at risk for AKI, and to further elucidate the biological mechanisms underlying the development of this outcome. This dissertation will leverage robust clinical electronic health record data to quantify those at greatest risk, and evaluate whether genetic profiles likewise have utility in this determination.

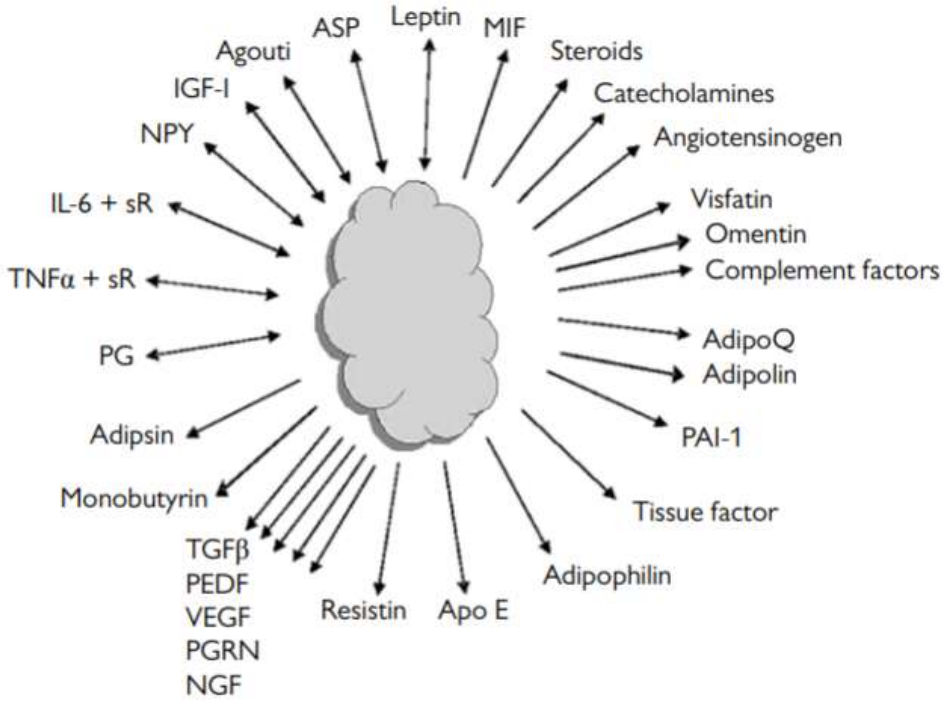


Figure 1.1. Hormones, cytokines, and other products of adipose tissue. ASP = acylation stimulating protein, MIF = macrophage migration inhibitory factor, PAI-1 = plasminogen activator inhibitor-1, Apo E = apolipoprotein E, TGF-β = transforming growth factor - beta, PEDF = pigment epithelium-derived factor, VEGF = vascular endothelial growth factor, PGRN = progranulin, NGF = nerve growth factor, PG = prostaglandin, TNFα + sR = tumor necrosis factor alpha and soluble receptors, IF-6 + sR = interleukin-6 and soluble receptors, NPY = neuropeptide Y, IGF-I = insulin growth factor I. Figure from Smitka K, Marešová D. Adipose Tissue as an Endocrine Organ: An Update on Pro-inflammatory and Anti-inflammatory Microenvironment. Prague Med Rep. 2015;116(2):87-111. doi:10.14712/23362936.2015.49.

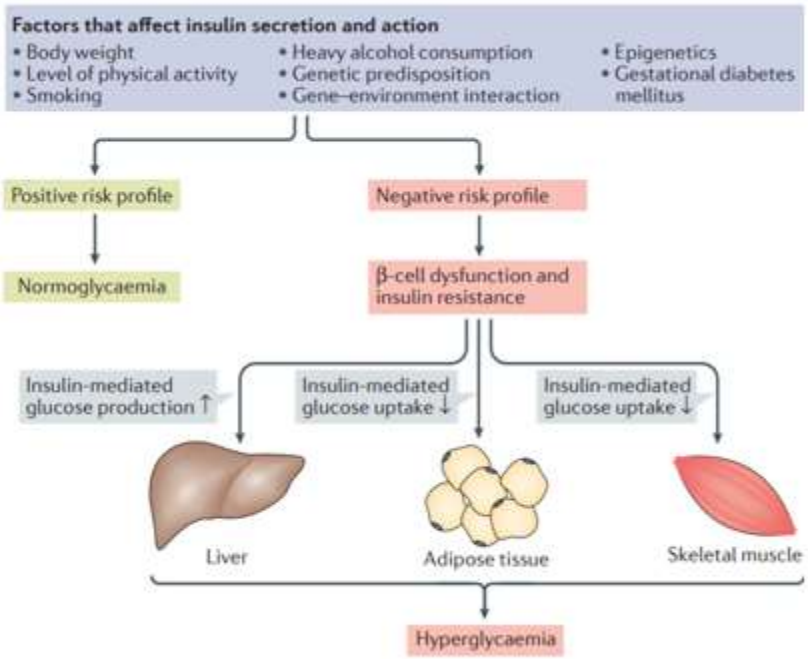


Figure 1.2. Pathophysiology of hyperglycemia. Figure from Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 02 2018;14(2):88-98. doi:10.1038/nrendo.2017.151.

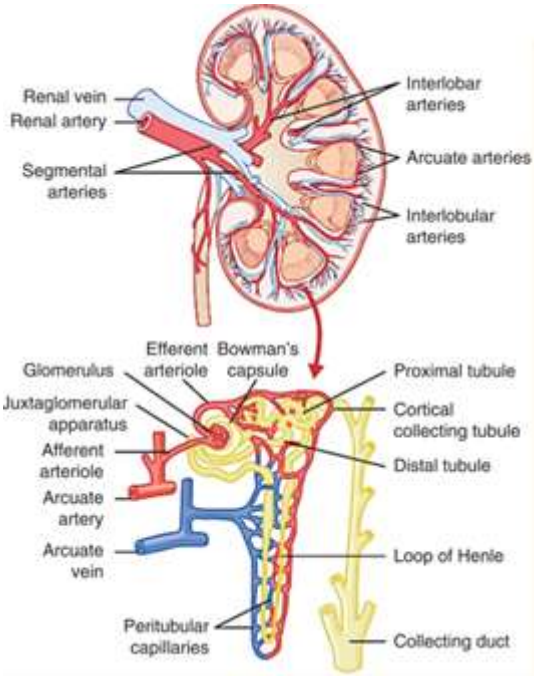


Figure 1.3. The anatomy of the kidney and a single nephron. Figure from Chade AR. Renal vascular structure and rarefaction. Compr Physiol. Apr 2013;3(2):817-31. doi:10.1002/cphy.c120012.

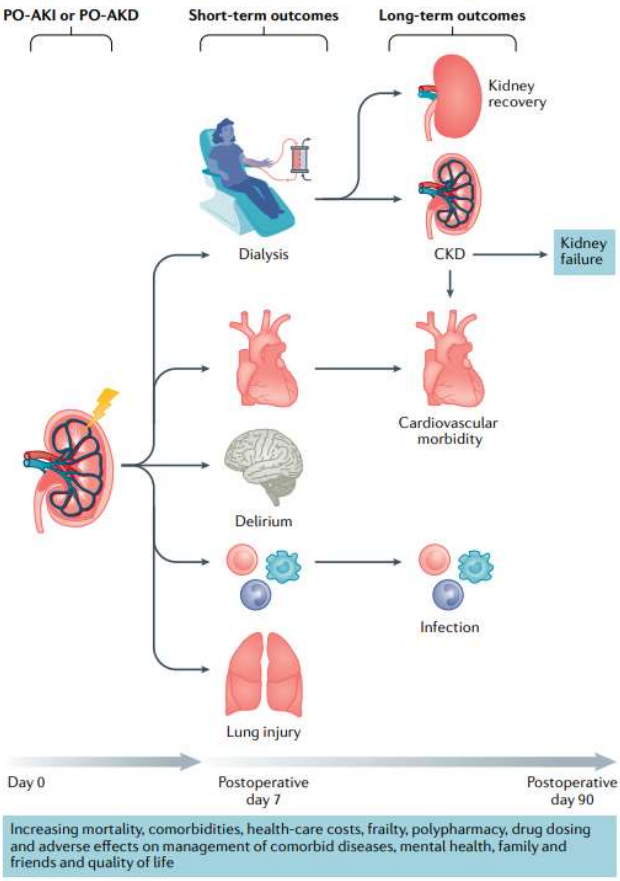


Figure 1.4. Outcomes of postoperative acute kidney injury (PO-AKI) and postoperative acute kidney disease (PO-AKD). CKD = chronic kidney disease. Figure from Prowle JR, Forni LG, Bell M, et al. Postoperative acute kidney injury in adult non-cardiac surgery: joint consensus report of the Acute Disease Quality Initiative and PeriOperative Quality Initiative. Nat Rev Nephrol. 09 2021;17(9):605-618. doi:10.1038/s41581-021-00418-2.

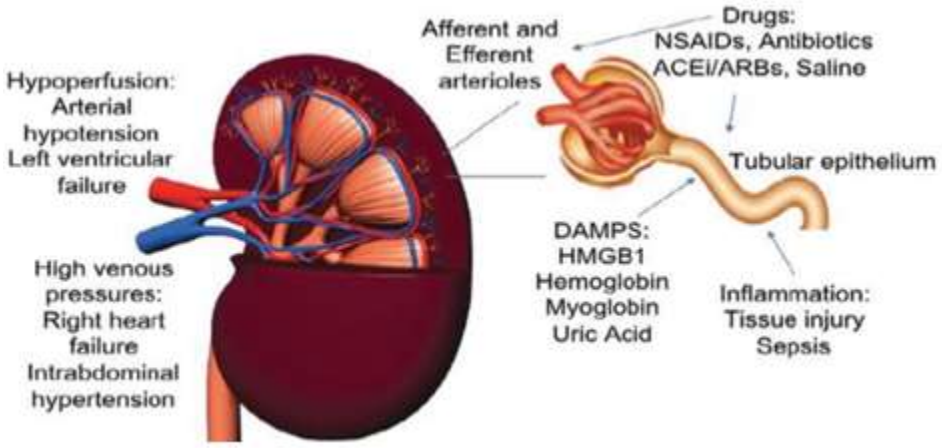


Figure 1.5. Mechanisms of acute kidney injury in the intraoperative setting. NSAID = non-steroidal anti-inflammatory drugs, ACEi = angiotensin-converting enzyme inhibitors, ARB = angiotensin II receptor blockers, DAMPS = damage-associated molecular patterns, HMGB1 = high mobility group box protein I. Figure from Zarbock A, Koyner JL, Hoste EAJ, Kellum JA. Update on Perioperative Acute Kidney Injury. Anesth Analg. 11 2018;127(5):1236-1245. doi:10.1213/ANE.0000000000003741.

Chapter 2

Patterns of Cardiometabolic Disease and Obesity Differentially Predict Acute Kidney Injury Following Joint Replacement

2.1. Abstract

Introduction: Total joint arthroplasty is the most common elective surgery performed in the United States. There is a paucity of information describing cardiometabolic disease patterns, obesity, and associations with postoperative acute kidney injury (AKI). This study aims to describe the co-occurrence of cardiometabolic diseases with and without obesity and analyze associated risks of postoperative AKI following total knee and hip arthroplasty procedures.

Methods: This retrospective analysis examined patients ≥18 years of age undergoing primary non-emergent total knee or hip arthroplasties across academic and community health systems within the Multicenter Perioperative Outcomes Group between 2008 and 2019. AKI was defined based upon postoperative creatinine values using modified KDIGO criteria. The primary outcome was any AKI stage ≥1. Cardiometabolic diseases were defined using ICD 9/10 codes, preoperative vital signs and labs, and preoperative history and physical data. Latent classes were constructed from cardiometabolic diseases including hypertension, diabetes, and coronary artery disease. Following latent class construction, the data was split 70/30 into derivation and validation datasets at the institution level. A mixed-effect logistic regression model was constructed, adjusting for random effect of institution, the AKI outcome, and the interaction

between latent class membership and obesity status, adjusting for additional known risk factors for AKI. Model fixed effects were then applied in the validation cohort and model area under the curve (AUC) c-statistics.

Results: Of the 81,871 cases meeting study inclusion criteria, 4,023 (4.9%) developed AKI. Compared to those without AKI, those with AKI were more commonly older and with higher BMI and ASA physical classification scores. A latent class model selected three groups of cardiometabolic disease patterns, labeled as "Hypertension (HTN) Only", "Metabolic Syndrome (MetS)", and "MetS+Cardiovascular Disease (CVD)". There was no significant difference in class membership by AKI status between derivation and validation cohorts. After model adjustment, varying combinations of latent classes and obesity status yielded differential risk of AKI compared to those in "HTN Only"/Non-obese". Those "HTN Only"/Obese had 1.7-fold increased odds of AKI compared to "HTN Only"/Non-obese (95%CI: 1.5-2.0). Compared to "HTN Only"/Non-obese, those "MetS+CVD"/Obese had the highest odds of AKI (OR 3.6, 95%CI: 3.1-4.3), while "MetS+CVD"/Non-obese had 2.5 times the odds of AKI (95%CI: 2.0-3.0). The model performed well in both cohorts (AUC 0.748 derivation, 0.732 validation).

Conclusion: There exists significant heterogeneity in the odds of AKI given the presence of comorbid cardiometabolic disease with or without obesity. The use of latent classes intersected with obesity can prove a useful tool for clinicians to determine who is most at risk for AKI following elective joint replacement.

2.2. Background

Total joint arthroplasty (TJA) is the most common elective surgery performed in the United States[102,103]. From 2014 to 2030, the expected number of TJA procedures is expected to rise by 129% for hips and 182% for knees, resulting in a total of more than 2.5 million cases per year[104]. Because of the high burden of obesity and chronic conditions among those with osteoarthritis[104-108], and known surgical risks associated with comorbidities[13,109], questions remain about the safety of this elective procedure for some patients. While individuals with obesity have similar or better improvements in physical functioning and pain post-operatively than non-obese individuals[110,111], they have higher risks of adverse postoperative infections and complications including acute kidney injury (AKI)[13,109]. Acute kidney injury is a serious postoperative complication occurring in 2-8% of TJA procedures, and is associated with significant increases in hospital length of stay, postoperative mortality[112,113], and permanent decrease in kidney function[114].

Prior work has found that in a non-cardiac surgical population, obesity alone accounted for 60% increased odds of postoperative complications, and comorbid diabetes and hypertension resulted in an additional 100% increased odds. Single- and multi-center studies of both cardiac and non-cardiac surgical populations have shown these factors to be independent predictors of postoperative AKI[8,17-22]. With the increase in outpatient TJA procedures due to changes in Centers for Medicare and Medicaid reimbursement practices[115], fewer patients are staying under clinical observation for prolonged periods after surgery, thereby increasing the need to identify who is at higher risk for these adverse outcomes. However, no studies to date have specifically evaluated this joint relationship among patients undergoing TJA, the most common elective procedure, in a contemporary, multicenter cohort.

Given the projected increase in these surgeries in outpatient settings and a need to understand who is at greatest risk for postoperative complications, the aim of this study was to describe and analyze how cardiometabolic disorders cluster and to examine the association of these clusters with the risk of postoperative AKI. We hypothesized that there would be multiple clinically distinct clusters of patients including one generally healthy cluster. Additionally, we hypothesized that clusters with symptomology consistent with hypertension and diabetes would have the highest rates of postoperative AKI regardless of the presence of obesity.

2.3. Methods

Data for this study is from the Multicenter for Perioperative Outcomes Group (MPOG) database, which contains data from over 50 institutions across the country and 2 international sites. The University of Michigan Institutional Review Board approved this study with a waiver of informed consent (HUM00180603). The analytic sample includes patients ≥18 years of age presenting to a participating hospital for primary non-emergent total knee or hip arthroplasty (anesthesia current procedural terminology codes 01402 and 01214, respectively) from January 1, 2008 to December 31, 2019 with data of adequate quality for performing observational research (details in Appendix Table A.1). A free-text search of procedure text within the electronic medical records was conducted to validate inclusion for primary total knee and hip arthroplasty. The terms used for inclusion and exclusion in this search are in Appendix Table A.2.

Primary Outcome

The primary outcome was acute kidney injury (AKI). The criteria for this outcome are adapted from the validated Kidney Disease – Improving Global Outcomes (KDIGO) definition, which is a globally accepted standard for defining acute kidney injury[116]. For the purposes of this

study, the outcome of AKI will be defined as any KDIGO stage ≥1[14]; a postoperative creatinine within 7 days ≥ 1.5 times the baseline creatinine or the postoperative creatinine within 48 hours of anesthesia end ≥ 0.3 mg/dL above the baseline creatinine.

Exposure of Interest

The following pre-operative cardiometabolic conditions were extracted and considered in the construction of the latent classes: hypertension, hyperlipidemia/hypercholesterolemia, diabetes, peripheral vascular disease, systemic inflammatory conditions (i.e., systemic lupus erythematosus, rheumatoid arthritis, etc.), hypothyroidism, cardiac arrhythmia, congestive heart failure, and coronary artery disease. Obesity is an additional exposure of interest, but was not included in the latent class construction; the difference in risk of AKI for the cardiometabolic latent classes with and without obesity was the primary comparison of interest. All comorbidities were defined based on ICD 9/10 codes (including codes present on admission), relevant history and physical (H&P) elements, and preoperative laboratory or physiologic measurements, as appropriate. Definitions of each element are in Appendix Table A.3. Patients meeting any of the criteria for a given condition were coded as "yes" for that condition.

Covariates

Additional variables considered in analyses included age, gender, race, preoperative estimated glomerular filtration rate (eGFR), smoking status, year of case, and American Society of Anesthesiologists (ASA) physical status. ASA physical status is an overall physician assessment of patient health where a class of 1 indicates a healthy patient and a class of 4 indicates life-threatening severe systemic disease[117]. Intraoperative data collected included use of general anesthesia (yes/no), blood transfusions (yes/no), total fluid volume given, use of nephrotoxic medications (yes/no, use of non-steroidal anti-inflammatory medications,

antibiotics, or diuretics), use of tranexamic acid (yes/no) and intraoperative hypotension defined as the number of minutes with mean arterial pressure <65 mmHg[14].

Statistical Methodology

Descriptive statistics are presented as frequencies with percentages for categorical variables and either means with standard deviations or medians with interquartile ranges for continuous variables, as appropriate. Continuous data was assessed for normality using histograms, the Kolmogorov-Smirnov test, and Q-Q plots. Univariate comparisons between those with and without AKI were computed using chi-squared or Fisher's exact tests for categorical variables and independent t-tests or Wilcoxon rank-sum tests for continuous variables, as appropriate. Effect modification of latent classes by obesity status was examined. Standardized differences between those with and without AKI were computed. A p-value of 0.05 was considered statistically significant for all analyses. A complete case analysis was conducted. Analysis was conducted using SAS v. 9.4 (SAS Institute, Cary, NC) and RStudio version 1.4.

Latent Class Construction

A latent class analysis was conducted to determine if there is clustering present in the cardiometabolic diagnoses of interest, each considered as a binary variable. The latent class model estimates the probability of a particular response pattern in the contingency table of all observed variables using the formula:

$$P(\boldsymbol{Y} = \boldsymbol{y}) = \sum_{c=1}^{C} \gamma_c \prod_{j=1}^{J} \prod_{r_{j=1}}^{R_j} \rho_{j,r_j|c}^{I(y_j=r_j)}$$

where γ_c is the probably of membership in a given latent class c and $\rho_{j,r_j|c}^{I(y_j=r_j)}$ is the probability of response r_j to the observed variable (j) conditional on the membership in a particular latent class c[118]. Parameters for the model are estimated using maximum likelihood with expectation-

maximization. The vector of γ is the probabilities of latent class membership, which sum to 1. The matrix of ρ parameters are the item-response probabilities conditional on class membership.

The parametric bootstrap likelihood ratio test, computed using the SAS macro "LCABootstrap", was used to evaluate the adequacy of models and the number of classes that best fit the data[119]. This test compares the null hypothesis of a *k*-class LCA to that of the alternative hypothesis of a more adequate ($k + 1$) class LCA model. Bootstrapping is used to randomly sample the data multiple times and analyze both the null and alternative hypotheses. The bootstrapped p-value is defined as $(s + 1)/(B + 1)$ where s is the number of datasets having a likelihood ratio statistic larger than the observed sample and B is the total number of bootstrapped samples generated. For this analysis, we tested 3 and 4 latent classes. Final selection of the latent classes was based upon the likelihood ratio tests and the clinical utility of the classes. Latent class models were not adjusted for covariates. The distribution of posterior probabilities of class membership for assigned classes were assessed.

Final latent class membership was determined by applying a posterior probability of class membership for each participant based on the set of comorbidities present or not for that individual for the class size that best fits the data. Final class membership was mutually exclusive. This methodology was chosen over a one-step approach to allow for the multicenter structure of our data to be accounted for in the final outcome model of interest. Classes were labeled based on the rates of cardiometabolic conditions seen within the class. All latent class analyses were performed using the LCA procedure in SAS 9.4[118].

Given the variability of latent classes across populations, a series of sensitivity analyses for class construction were conducted (Appendix 2.2).

Derivation/Validation Dataset Construction

To examine the relationship between the latent classes of comorbidities and AKI, institutions were split randomly into a derivation (70%) and validation (30%) cohort. Of the 30 institutions included in the final analysis, 21 were included in the derivation dataset (70%) and 9 were included in the validation dataset (30%). Characteristics of both datasets can be found in Appendix Table A.4. Of the 55,798 cases in the derivation dataset, 2,689 (4.8%) had AKI. Of the 26,073 cases in the validation dataset, 1,334 (5.1%) had AKI. Appendix Table A.5 shows unadjusted odds of AKI for latent classes and interaction with obesity including a sensitivity analysis splitting data 50/50 within a given institution.

Multivariable regression models

Prior to model construction, collinearity between variables under consideration for model entry was assessed using Pearson correlation matrices ($r > 0.70$) and the variance inflation factor ($VIF > 10$). There was no significant collinearity detected in our sample.

Within the derivation cohort, a baseline logistic regression model was constructed to compare our data with current literature for the outcome of AKI stage 1+, adjusting for hypertension, high cholesterol, diabetes, obesity, peripheral vascular disease, rheumatoid arthritis and other inflammatory disorders, hypothyroidism, cardiac arrhythmias, congestive heart failure, coronary artery disease, age, sex, race, procedure type, ASA classification, smoking category, general anesthesia use, packed red blood cell use, crystalloid equivalents given, minutes of mean arterial hypotension < 65mmHg, preoperative hypotension, intraoperative nephrotoxic medication use, tranexamic acid use, and case year. In the baseline model including all covariates, in addition to all cardiometabolic comorbidities as separate variables, almost all of the conditions of interest were independent predictors of AKI (data not shown). The notable exceptions were high cholesterol and coronary artery disease, which did not have a statistically

significant association with AKI after adjustment (p = 0.981 and 0.4312, respectively). The fully adjusted model had a moderately high area under the receiver operating curve (AUROC) in the derivation dataset (0.758).

Then, generalized linear mixed models were constructed to evaluate the relationship between the latent classes, obesity, and the outcome of AKI. The final model was adjusted for age, sex, race, procedure type, ASA classification, smoking category, general anesthesia use, packed red blood cell use, crystalloid equivalents given, minutes of mean arterial hypotension < 65mmHg, preoperative hypotension, intraoperative nephrotoxic medication use, tranexamic acid use, and case year. All models included institution as a random effect, and the median odds ratio of the between-institution effect was computed[120]. A caterpillar plot of random effect intercepts is presented in Appendix Figure A.1. Sensitivity analyses were conducted within the following subgroups: general anesthesia, no general anesthesia, total knee replacement, and total hip replacement.

Model predictive capability was assessed using the area under the receiver operating curve c-statistic and precision-recall curves. Precision recall curves were computed using the R package "PPROC"[121]. The fixed effects from the fitted models within the derivation cohort were assessed for goodness of fit and predictive capability within the validation cohort.

Power Analysis

A logistic regression of a binary response variable (Y) on a binary independent variable (X) with a sample size of 21,593 observations (of which 75% are in the group X=0 and 25% are in the group X=1) achieves 80% power at a 0.050 significance level to detect a change in Prob(Y=1) from the baseline value of 0.050 to 0.040 between two latent classes. This change corresponds to an odds ratio of 0.792; based on findings in the literature with respect to risk

factors for AKI this odds ratio is reasonable to expect. An adjustment was made since a multiple regression of the independent variable of interest on the other independent variables in the logistic regression obtained an R-Squared of 0.150. Power was computed using PASS 2020 (PASS 2020 Power Analysis and Sample Size Software (2020). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass).

2.4. Results

The total analytic sample included 81,871 cases with total joint arthroplasty, representing 30 unique institutions (Figure 2.1). Basic demographic descriptive statistics of the analytic cohort both overall and stratified by AKI status are in Table 2.1. A total of 4,023 (4.9%) of patients had AKI, with an institutional range from 1.0% to 9.6%. Compared to those without AKI, those with AKI were slightly older, more frequently male and non-Hispanic Black, had a higher BMI and ASA physical classification scores.

There were important differences in the prevalence of many cardiometabolic conditions by AKI status. Patients with AKI had a higher prevalence of hypertension, peripheral vascular disorders, diabetes, cardiac arrhythmias, congestive heart failure, and obesity (Table 2.1).

Latent Class Construction

Although the parametric bootstrap likelihood ratio test determined that statistically the 4-class model was a better fit for the data ($p = 0.002$), the 3-class model was chosen for primary data reporting given its ease of clinical use as a simpler classification.

In the three-class model, groups with clinically distinct presentation were identified (Figure 2.2; 4-class model presented in Appendix Figure B). The three classes include: (1) a "hypertension only" class representing 45.2% (n = 37,032) of the population with moderate probability of hypertension and low probability of other factors (labeled “HTN only”); (2) a

"metabolic syndrome" class representing 45.1% (n=36,889) of the population with high probability of hypertension and high cholesterol and moderate probability of diabetes (labeled "MetS"); and (3) a "metabolic syndrome with cardiovascular disease" class representing 9.7% (n=7,950) of the population with high probability of hypertension, high cholesterol, cardiac arrhythmias, coronary artery disease (CAD), and congestive heart failure (CHF), and moderate probability of diabetes and peripheral vascular disease (labeled "MetS+CVD)"). Latent classes had generally high mean posterior probability of class membership and were stable across validation analyses (Appendix B).

Characteristics for individual latent class groups for three-class models can be found in Table 2.2. There were clinically meaningful differences in age, ASA status, and obesity status between the cardiometabolic latent classes. Those in the "HTN only" class were younger, had lower ASA status, and were less likely to be obese as compared to patients in other classes. There were minimal differences between intraoperative characteristics across the latent class groups. Additionally, there were significant differences in AKI burden across the latent classes (Appendix Table A.6). Individuals in the "MetS" class had twice the odds of AKI (UOR 2.0, 95%CI: 1.8, 2.1) and those in the "MetS+CVD" class had 4.5 times the odds of AKI (UOR 4.6, 95%CI: 4.2, 5.0) as compared to those in the "HTN only" class.

Within each latent class, those with obesity had 30-90% higher odds of AKI than those without obesity (Appendix Table A.7). An interaction between latent class and obesity status demonstrated that those in the "HTN only" class and without obesity had the lowest odds of AKI as compared to all other class and obesity groups (Appendix Table A.6). The greatest burden of AKI was among those in the "MetS+CVD" class and with obesity; these individuals had more

than 7-fold increased odds of AKI (UOR 7.3 (95%CI: 6.4, 8.3) as compared to those in "HTN only" and without obesity.

Multivariable Model Results

In the adjusted model, compared to the "Hypertension Only/Non-obese", those in "Hypertension Only/Obese" had 1.7 times the odds of AKI (95%CI: 1.5, 2.0; Figure 2.3). Compared to "Hypertension Only/Non-obese", those in the "MetS/Non-obese" group had 1.4 times the odds of AKI (95%CI: 1.1, 1.6) and those in the "MetS/Obese" group had 2.5 times the odds (95%CI: 2.2, 2.9). Compared to "Hypertension Only/Non-obese", those in the "MetS+CVD/Non-obese" group had 2.5 times the odds of AKI (95%CI: 2.0, 3.0) and those in the "MetS+CVD/Obese" group had 3.6 times the odds of AKI (95%CI: 3.1, 4.3). These results were significantly attenuated from the unadjusted model containing just the interaction between obesity and latent class. Similar results were seen in all sensitivity analyses (data not shown).

The fully adjusted model had a moderately high area under the receiver operating curve (AUROC) in the derivation dataset (0.748) and had only slight attenuation in the validation dataset (AUROC = 0.732). The PRC showed slight attenuation between derivation and validation datasets (0.139 vs. 0.132, respectively). The MOR for this model in the derivation cohort was 1.63.

2.5. Discussion

In this multicenter cohort of elective total knee and hip arthroplasty patients, obesity and cardiovascular disease were associated with increased risk of AKI following surgery, but the magnitude of risk varied by patterning of cardiometabolic diseases and obesity status. Most notably, individuals with more significant comorbid disease had higher odds of AKI regardless of the presence of obesity. This suggests that while obesity may play a role in risk of

postoperative AKI, the effect of cardiometabolic comorbidity regardless of obesity status may have value in clinical decision-making.

Studies examining postoperative risk of AKI in non-cardiac surgical cohorts have found that diabetes, cardiovascular disease, and obesity are independent risk factors for the outcome, with those having these individual conditions at approximately 1-2 times the risk of AKI compared to those without[8,14,122,123]. These studies, however, do not account for joint presentation of these conditions. Indeed, cardiovascular comorbidity has been rarely examined in the postoperative setting. Studies that have looked at these conditions jointly are widely limited to only examining the metabolic syndrome. One such study of 310,000 general non-cardiac surgical patients classified metabolic syndrome as a patient having all of obesity (defined using BMI $\geq$ 30), diabetes, and hypertension[13]. Compared to normal weight individuals, they found that those with obesity (without both hypertension and diabetes) had at least a 1.6-fold increased risk of progressive renal insufficiency or acute renal failure, while those with metabolic syndrome had at least a 3.3-fold increased risk of the outcome[13]. Our study results showed a similar though slightly attenuated elevation of risk when latent classes were used rather than a hard metabolic syndrome classification.

Latent class analysis is an approach where an algorithm is deployed in an unsupervised fashion (without *a priori* definitions of classification) to ascertain the natural groups or clusters that arise from within the population[124]. Our latent class analyses were able to derive meaningful classes of individuals consistent with intuitive clinical presentation of cardiometabolic comorbidity. The classes were robust across sensitivity analyses and performed well when implemented within the validation cohort, suggesting that these groups are naturally present within this surgical cohort. Biologically, the latent classes derived appear to be snapshots of the

known progression of cardiometabolic conditions. Obesity is a known risk factor for diabetes, hypertension, high cholesterol, and even those thought to be metabolically healthy obese may not remain that way[25,125]. Additionally, conditions associated with the metabolic syndrome can lead to cardiovascular sequelae including cardiac arrhythmias, congestive heart failure, peripheral vascular disease, and coronary artery disease[24,68,69,73]. While the cross-sectional nature of the current study cannot assess temporality of these diagnoses, the increased risk for AKI for those with greater comorbidity is suggestive of a more prolonged disease course with systemic inflammatory damage, possibly indicative of poor control of these conditions. Future prospective studies could examine the duration and clinical markers of these conditions and how these factors may influence AKI risk.

A major strength of this study lies in the multicenter nature of the dataset, which allows for the examination of a relatively rare condition following outpatient joint replacement. Differences in institutional practice and populations from sites across the United States increase the generalizability of the findings to other total joint arthroplasty populations; however, the results may not be generalizable to other surgical types. Data collection from multiple sources for cardiometabolic comorbidities and inclusion of important covariates contributed to the robust analyses conducted, and innovative methodology was used to consider the effect of cardiometabolic conditions on risk of AKI.

This study, however, does have some potential limitations. Due to the retrospective nature of the data, there may be under-reporting of some of the clinical conditions. This concern was mitigated by using multiple definitions for each comorbidity to capture as many likely cases as possible. There is the potential for bias in the construction of the latent classes due to the inherent uncertainty around class membership. Given software limitations in the construction of

generalized linear mixed models utilizing latent classes, our modeling was unable to account for this uncertainty, potentially leading to an underestimate of the variance and increases in false positives and error. This methodology could lead results to be biased both towards and away from the null, depending on the other potential class assignments for a given individual. However, our sensitivity analyses showed that within the low percentage of individuals who were assigned a different latent class in the validation, almost everyone was placed in a class with more significant comorbidity in the validation than in the full analytic cohort; this could potentially lead the results of our main analysis to be an underestimate of the true effect. Additionally, institutional practice patterns may limit those who get certain non-urgent elective surgeries, especially joint replacement, to healthier populations, making it more difficult to accurately assess associations between comorbidities and the outcome. This practice introduces selection bias at the hospital level, and as a result downstream selection bias into the resulting analytic cohort, with differential likelihood of being in the analytic cohort changing based on healthcare system. For a single center study, this bias could significantly attenuate the results as more individuals who developed AKI in the sample would be healthier, an effect compounded by small sample size of the outcome. Results from such studies may not be generalizable to institutions with broader inclusion criteria for these surgeries. However, within our sample this selection bias is less of a concern given 30 institutions were included, accounting for a variety of arthroplasty surgical inclusion criteria and a range of rates of AKI. Future work should be conducted to assess the influence of selection bias at the hospital level on the results from studies such as this.

2.6. Conclusion

There exists significant heterogeneity in the odds of AKI given the presence of comorbid cardiometabolic disease with or without obesity. The use of latent classes intersected with obesity can prove a useful tool for clinicians to determine who is most at risk for AKI following elective joint replacement.

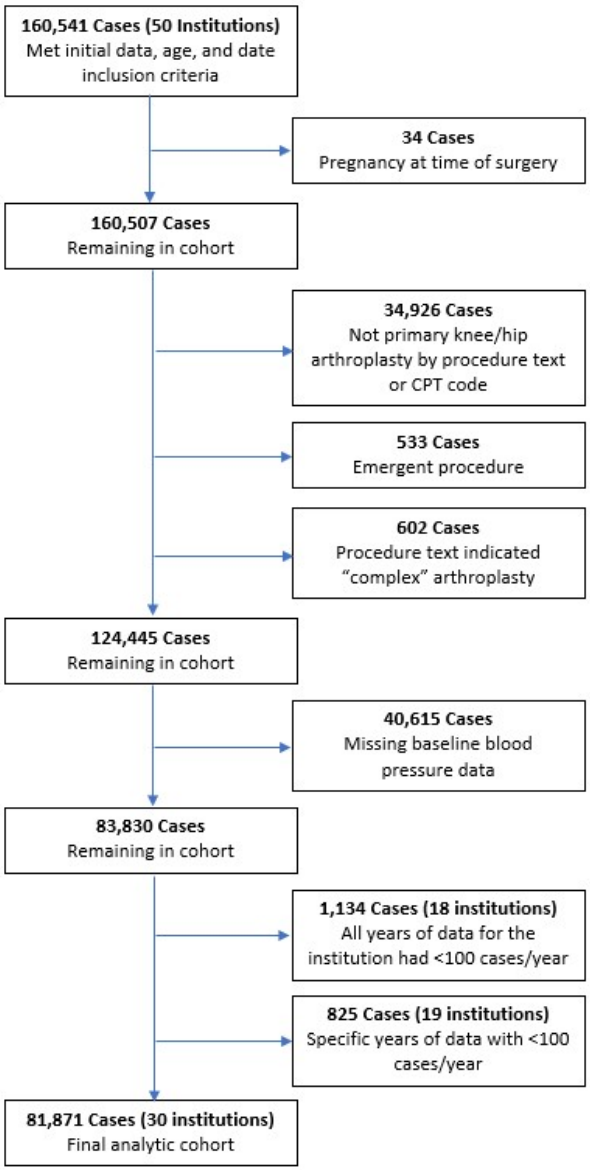


Figure 2.1. Study inclusion flow chart

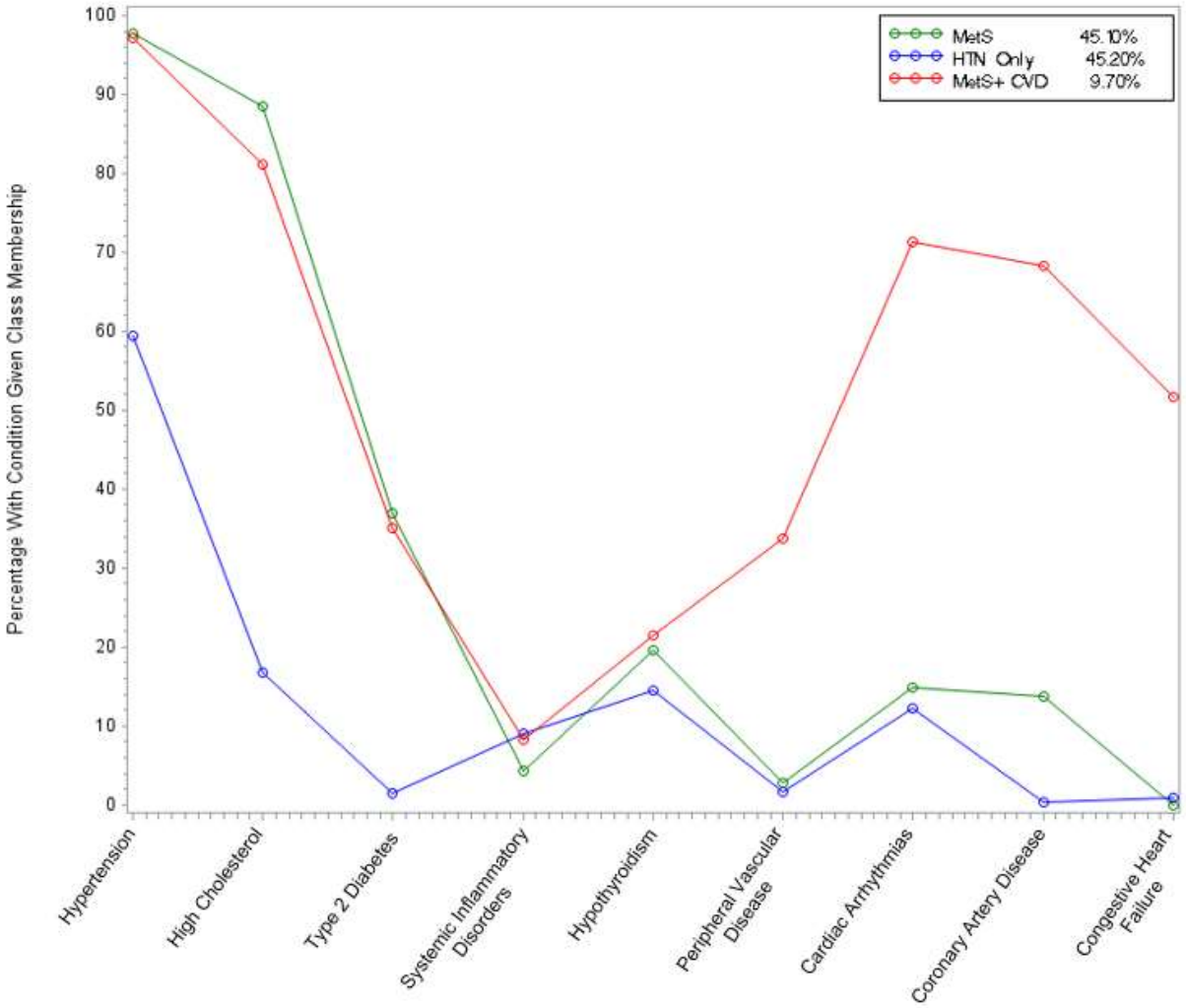


Figure 2.2. Percentage of cases with a cardiometabolic condition given class membership for the three-class latent class model. Abbreviations: MetS – Metabolic Syndrome, HTN – Hypertension, CVD – Cardiovascular Disease

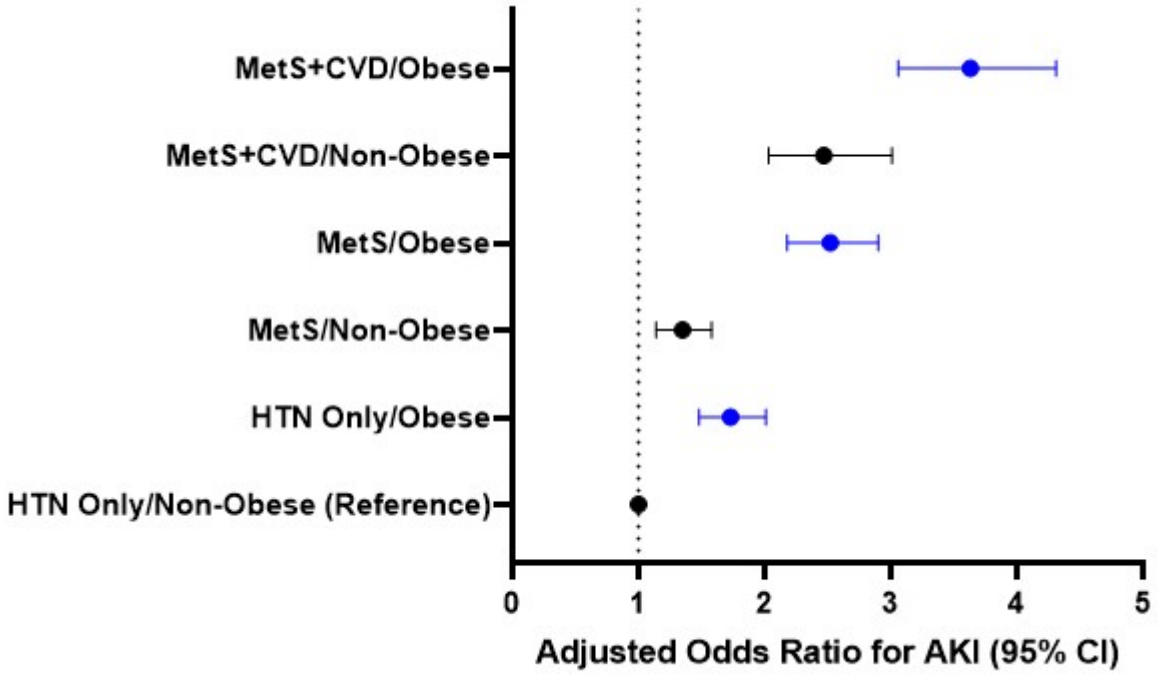


Figure 2.3. Forest plot of results of fully adjusted model within the derivation dataset (N = 55,798) for the interaction of latent class membership and obesity, with the reference group of "HTN Only"/Non-obese. Odds ratios for obese individuals are in blue. Model was adjusted for the random effect of institution, and additionally adjusted for fixed effects of age, sex, race, procedure type (knee versus hip), ASA classification, smoking category, general anesthesia use, packed red blood cell use, crystalloid equivalents given, minutes of mean arterial hypotension <65mmHg, preoperative hypotension, intraoperative nephrotoxic medication use, tranexamic acid use, and case year. Abbreviations: MetS – Metabolic Syndrome, CVD – Cardiovascular Disease, HTN - Hypertension

Table 2.1. Demographic characteristics of total knee and hip arthroplasty patients

	Overall (N = 81,871)	No Acute Kidney Injury (N = 77,848)	Any Acute Kidney Injury (N = 4,023)	Absolute Standardized Differences
Demographics				
Age Group (years)				0.239
18-29	519 (0.6)	505 (0.7)	14 (0.4)	
30-39	1,100 (1.3)	1,079 (1.4)	21 (0.5)	
40-49	4,321 (5.3)	4,199 (5.4)	122 (3.0)	
50-59	16,467 (20.1)	15,816 (20.3)	651 (16.2)	
60-69	29,363 (35.9)	27,954 (35.9)	1,409 (35.0)	
70-79	22,770 (27.8)	21,497 (27.6)	1,273 (31.6)	
80+	7,331 (9.0)	6,798 (8.7)	533 (13.3)	
Body Mass Index (kg/m2)	31.4 ± 6.8	31.2 ± 6.7	34.1 ± 7.6	0.397
Gender				0.107
Male	32,758 (40.0)	30,946 (39.8)	1,812 (45.0)	
Female	49,113 (60.0)	46,902 (60.2)	2,211 (55.0)	
Race				0.299
Non-Hispanic White	61,888 (75.6)	59,243 (76.1)	2,645 (65.8)	
Non-Hispanic Black	11,019 (13.5)	10,038 (12.9)	981 (24.4)	
Hispanic	840 (1.0)	797 (1.0)	43 (1.1)	
Other	8,124 (9.9)	7,770 (10.0)	354 (8.8)	
ASA Class				0.568
1	1,525 (1.9)	1,510 (1.9)	15 (0.4)	
2	39,013 (47.7)	37,989 (48.8)	1,024 (25.5)	
3	39,717 (48.5)	37,012 (47.5)	2,705 (67.2)	
4	1,616 (2.0)	1,337 (1.7)	279 (6.9)	
Smoking Status				0.027
Current Smoker	7,544 (9.2)	7,074 (9.1)	470 (11.7)	
Former Smoker	1,962 (2.4)	1,858 (2.4)	104 (2.6)	
Never Smoker	9,739 (11.9)	9,375 (12.0)	364 (9.1)	
Unknown	62,626 (76.5)	59,541 (76.5)	3,085 (76.7)	
Cardiometabolic Conditions for Latent Class Analysis				
Hypertension	65,791 (80.4)	62,001 (79.6)	3,790 (94.2)	0.443
Hyperlipidemia/ Hypercholesterolemia	45,304 (55.3)	42,716 (54.9)	2,588 (64.3)	0.194
Peripheral Vascular Disorders	4,355 (5.3)	3,929 (5.1)	426 (10.6)	0.208
Diabetes	16,925 (20.7)	15,436 (19.8)	1,489 (37.0)	0.388
Systemic Inflammatory Disorders	5,593 (6.8)	5,321 (6.8)	272(6.8)	0.003
Hypothyroidism	14,292 (17.5)	13,470 (17.3)	822 (20.4)	0.080
Cardiac Arrhythmias	15,760 (19.3)	14,562 (18.7)	1,198 (29.8)	0.261
Congestive Heart Failure	4,429 (5.4)	3,794 (4.9)	635 (15.8)	0.364
Coronary Artery Disease	10,594 (12.9)	9,629 (12.4)	965 (24.0)	0.305
Additional Comorbidities				

Obesity	45,214 (55.2)	42,404 (54.5)	2,810 (69.9)	0.321
Preoperative Hypotension	16,347 (20.0)	15,208 (19.5)	1,139 (28.3)	0.207
Estimated Glomerular Filtration Rate	78.3 ± 22.4	78.8 ± 22.0	68.9 ± 27.1	0.402
Intraoperative Characteristics				
Procedure Type				0.027
Knee	46,662 (57.0)	44,420 (57.1)	2,242 (55.7)	
Hip	35,209 (43.0)	33,428 (42.9)	1,781 (44.3)	
Use of General Anesthesia	30,721 (37.5)	28,684 (36.9)	2,037 (50.6)	0.281
Packed Red Blood Cell Transfusion	531 (0.7)	450 (0.6)	81 (2.0)	0.127
Total Fluid Volume, Crystalloid Equivalents	1559.5 ± 1277.2	1559.5 ± 1289.9	1558.2 ± 998.2	0.001
Minutes of MAP <65	3.0 [0.0 to 13.0]	3.0 [0.0 to 13.0]	3.0 [0.0 to 12.0]	0.048
Tranexamic acid use	54,461 (66.5)	52,079 (66.9)	2,382 (59.2)	0.160
Nephrotoxic Medication Use	72,738 (88.8)	69,133 (88.8)	3,605 (89.6)	0.026
Diuretic	67 (0.1)	57 (0.1)	10 (0.3)	0.044
Antibiotic	71,998 (87.9)	68,427 (87.9)	3,561 (88.5)	0.019
NSAID	9,569 (11.7)	9,184 (11.8)	385 (9.6)	0.072

Data are presented as means ± standard deviations, medians [25th percentile to 75th percentile], or frequency (percentage) as appropriate. A standardized difference >0.20 indicates the potential for heterogeneity between those with and without AKI

Table 2.2. Demographic characteristics of total knee and hip arthroplasty patients, derivation and validation cohorts

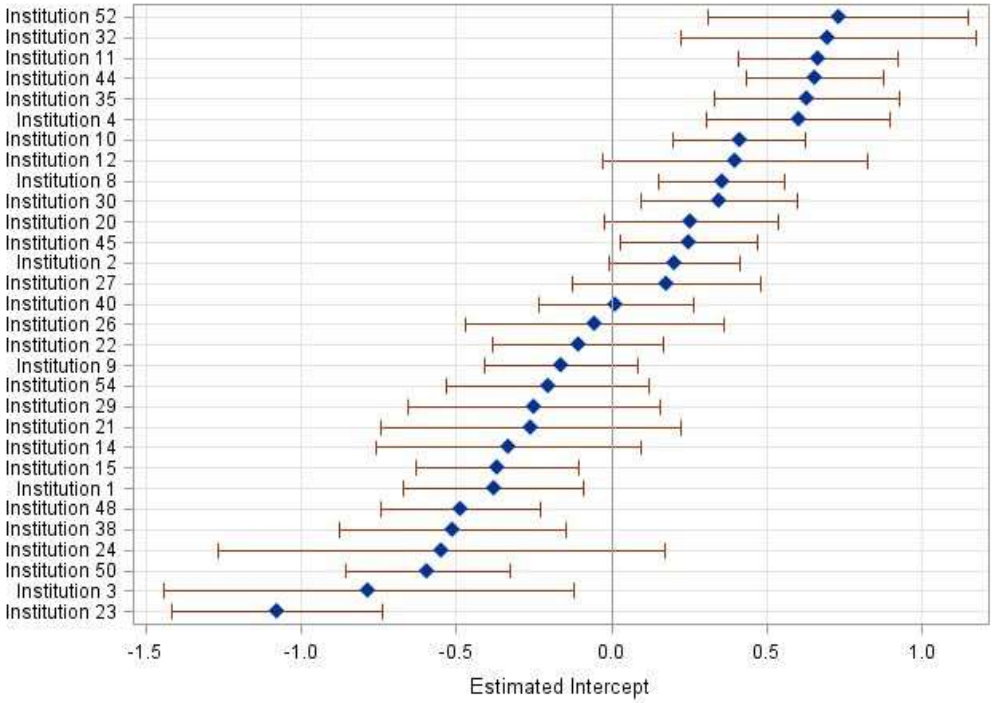
	DERIVATION DATASET			VALIDATION DATASET		
	MetS (N = 24,945)	**Hypertension Only (N = 25,575)**	**MetS and CVD (N = 5,278)**	**MetS (N = 11,944)**	**Hypertension Only (N = 11,457)**	**MetS and CVD (N = 2,672)**
Demographics						
Age						
18-29	22 (0.1)	318 (1.2)	7 (0.1)	15 (0.1)	155 (1.4)	2 (0.1)
30-39	85 (0.3)	638 (2.5)	8 (0.2)	37 (0.3)	329 (2.9)	3 (0.1)
40-49	602 (2.4)	2,137 (8.4)	60 (1.1)	399 (3.3)	1,086 (9.5)	37 (1.4)
50-59	3,882 (15.6)	6,367 (24.9)	410 (7.8)	2,215 (18.5)	3,304 (28.8)	289 (10.8)
60-69	9,353 (37.5)	9,064 (35.4)	1,540 (29.2)	4,628 (38.8)	3,945 (34.4)	833 (31.2)
70-79	8,413 (33.7)	5,388 (21.1)	2,148 (40.7)	3,655 (30.6)	2,132 (18.6)	1,034 (38.7)
80+	2,588 (10.4)	1,663 (6.5)	1,105 (20.9)	995 (8.3)	506 (4.4)	474 (17.7)
BMI	32.1 ± 6.5	30.3 ± 6.7	31.5 ± 6.5	32.6 ± 6.8	30.7 ± 7.1	32.1 ± 6.8
Gender						
Male	10,235 (41.0)	9,312 (36.4)	2,964 (56.2)	4,709 (39.4)	4,081 (35.6)	1,457 (54.5)
Female	14,710 (59.0)	16,263 (63.6)	2,314 (43.8)	7,235 (60.6)	7,376 (64.4)	1,215 (45.5)
Race						
Non-Hispanic White	19,542 (78.3)	19,825 (77.5)	4,329 (82.0)	8,095 (67.8)	8,077 (70.5)	2,020 (75.6)
Non-Hispanic Black	2,350 (9.4)	2,294 (9.0)	451 (8.5)	2,887 (24.2)	2,505 (21.9)	532 (19.9)
Hispanic	237 (1.0)	247 (1.0)	39 (0.7)	150 (1.3)	140 (1.2)	27 (1.0)
Other	2,816 (11.3)	3,209 (12.6)	459 (8.7)	812 (6.8)	735 (6.4)	93 (3.5)
ASA Class						
1	118 (0.5)	963 (3.8)	1 (0.0)	43 (0.4)	399 (3.5)	1 (0.0)
2	9,999 (40.1)	14,972 (58.5)	443 (8.4)	5,688 (47.6)	7,530 (65.7)	381 (14.3)
3	14,360 (57.6)	9,385 (36.7)	4,216 (79.9)	6,125 (51.3)	3,489 (30.5)	2,142 (80.2)
4	468 (1.9)	255 (1.0)	618 (11.7)	88 (0.7)	39 (0.3)	148 (5.5)
Smoking Status						
Current Smoker	1,492 (6.0)	1,743 (6.8)	384 (7.3)	1,813 (15.2)	1,686 (14.7)	426 (15.9)
Former Smoker	767 (3.1)	584 (2.3)	233 (4.4)	187 (1.6)	130 (1.1)	61 (2.3)
Never Smoker	2,417 (9.7)	2,418 (9.5)	422 (8.0)	2,006 (16.8)	2,031 (17.7)	445 (16.7)
Unknown	20,269 (81.3)	20,830 (81.5)	4,239 (80.3)	7,938 (66.5)	7,610 (66.4)	1,740 (65.1)
Cardiometabolic Conditions for Latent Class Analysis						
Hypertension	24,434 (98.0)	16,043 (62.7)	5,139 (97.4)	11,612 (97.2)	5,983 (52.2)	2,580 (96.6)
Hyperlipidemia/ Hypercholesterolemia	21,989 (88.2)	3,523 (13.8)	4,261 (80.7)	10,670 (89.3)	2,668 (23.3)	2,193 (82.1)
Peripheral Vascular Disorders	645 (2.6)	403 (1.6)	1,711 (32.4)	386 (3.2)	234 (2.0)	976 (36.5)
Diabetes	9,033 (36.2)	346 (1.4)	1,873 (35.5)	4,596 (38.5)	159 (1.4)	918 (34.4)
Systemic Inflammatory Disorders	1,079 (4.3)	2,280 (8.9)	434 (8.2)	517 (4.3)	1,061 (9.3)	222 (8.3)
Hypothyroidism	5,144 (20.6)	3,811 (14.9)	1,167 (22.1)	2,080 (17.4)	1,556 (13.6)	534 (20.0)
Cardiac Arrhythmias	3,602 (14.4)	3,064 (12.0)	3,752 (71.1)	1,910 (16.0)	1,506 (13.1)	1,926 (72.1)
Congestive Heart Failure	0 (0.0)	217 (0.9)	2,756 (52.2)	0 (0.0)	108 (0.9)	1,348 (50.5)

Coronary Artery Disease	3,584 (14.4)	98 (0.4)	3,585 (67.9)	1,457 (12.2)	37 (0.3)	1,833 (68.6)
Additional Comorbidities						
Obesity	15,127 (60.6)	11,843 (46.3)	3,121 (59.1)	7,732 (64.7)	5,721 (49.9)	1,670 (62.5)
Preoperative Hypotension	3,329 (13.4)	3,850 (15.1)	1,178 (22.3)	3,334 (27.9)	3,758 (32.8)	898 (33.6)
Estimated Glomerular Filtration Rate	75.6 ± 21.6	81.8 ± 22.0	68.5 ± 22.7	77.3 ± 22.0	83.8 ± 22.4	70.5 ± 22.2
Intraoperative Characteristics						
Procedure Type						
Knee	15,382 (61.7)	13,334 (52.1)	3,024 (57.3)	7,441 (62.3)	5,923 (51.7)	1,558 (58.3)
Hip	9,563 (38.3)	12,241 (47.9)	2,254 (42.7)	4,503 (37.7)	5,534 (48.3)	1,114 (41.7)
Use of General Anesthesia	9,578 (38.4)	10,329 (40.4)	2,420 (45.9)	3,780 (31.7)	3,566 (31.1)	1,048 (39.2)
Packed Red Blood Cell Transfusion	124 (0.5)	188 (0.7)	78 (1.5)	55 (0.5)	54 (0.5)	32 (1.2)
Total Fluid Volume, Crystalloid Equivalents	1,545.1 ± 947.2	1,594.5 ± 1,637.1	1,484.9 ± 1,023.1	1,499.5 ± 977.7	1,633.0 ± 1,399.9	1,459.7 ± 1,065.8
Minutes of MAP <65	3.0 [0.0 to 13.0]	5.0 [0.0 to 15.0]	3.0 [0.0 to 11.0]	2.0 [0.0 to 11.0]	3.0 [0.0 to 14.0]	0.0 [0.0 to 9.0]
Tranexamic acid use	15,169 (60.8)	15,599 (61.0)	2,819 (53.4)	9,578 (80.2)	9,785 (85.4)	1,511 (56.6)
Nephrotoxic Medication Use	21,689 (87.0)	22,274 (87.1)	4,688 (88.8)	11,039 (92.4)	10,624 (92.7)	2,424 (90.7)
Diuretic	15 (0.1)	15 (0.1)	21 (0.4)	5 (0.0)	5 (0.0)	6 (0.2)
Antibiotic	21,543 (86.4)	22,166 (86.7)	4,663 (88.4)	10,852 (90.9)	10,379 (90.6)	2,385 (89.3)
NSAID	1,841 (7.4)	1,693 (6.6)	356 (6.7)	2,430 (20.3)	2,774 (24.2)	475 (17.8)

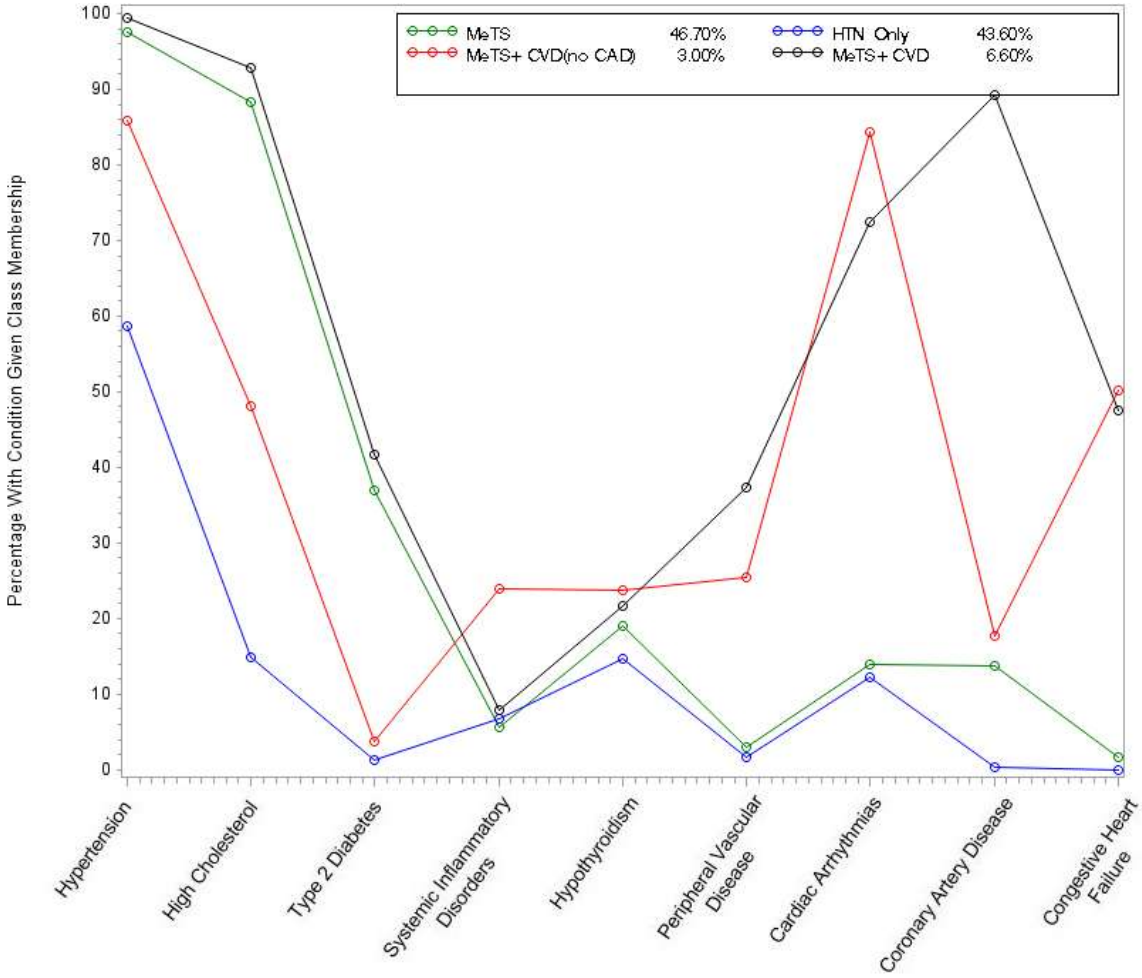
Data are presented as either mean ± standard deviation, median [25th to 75th percentile] or frequency (percentage of non-missing data). Abbreviations: MetS – metabolic syndrome, CVD – cardiovascular disease, CAD – coronary artery disease

Appendix A

Supplemental Material



Appendix Figure A.1. Caterpillar plot of estimated intercept parameters for the random effect of institution in the null model of acute kidney injury



Appendix Figure A.2. Percentage of cases with a cardiometabolic condition given class membership for the four-class latent class model. The main difference between three-class and four-class latent class models is the breakout of the MetS+CVD group into those with and without CAD. Abbreviations: MetS – Metabolic Syndrome, HTN – Hypertension, CVD – Cardiovascular Disease, CAD – Coronary Artery Disease.

Appendix Table A.1. Multicenter Perioperative Outcomes Group perioperative research standards

1. Has Valid Anesthesia Start time
2. Has Valid Anesthesia End time
3. Has a Valid Institution ID
4. Case Duration >15 minutes if Anesthesia Technique General = true
5. Case Duration >5 minutes if Anesthesia Technique General = false
6. Has an actual or predicted anesthesia CPT code
7. Has Age data
8. Has Sex data
9. Has valid ASA Class
10. Has Baseline Blood Pressure Mean
11. Has at least one intraoperative med administered
12. Has at least one ICD 9/10 discharge diagnoses
13. Has at least one creatinine or hematocrit within 365 days before/after surgery

Appendix Table A.2. Inclusion and exclusion search terms used for the free-text search of actual procedure text.

	Free-Text Search Terms
Exclusions	
Revisions/Conversions/Bilateral	revision | previous hip | explant | stage | bilateral | reimplantation | partial | redo | replant | conversion | rev | reimplant | convert | bilat | re-implant
Infection/Removal/Wound treatment	spacer | antibiotic spacer | infected | insertion drug | removal knee prosthesis | implant | drainage | wound/wound therapy | dehiscence | fasciotomy | i & d (and variants) | exchange | 11981 | core decompression | left explaint + spascer | remove total knee arthroplasty components
Hip Fracture	open fx/dislocation | debridement | open treatment | internal fixation | orif | open reduction | nail | foreign body removal | reconstruction | fixation | fusion | resection | hardware removal | remove hardware | removal | screw
Cancer Removal	radical resection | tumor | excision | flap | biopsy | curettage
Other	unlisted procedure | hemiarthroplasty | vac dressing change | amputation | osteotomy | percutaneous placement | acetabuloplasty | resurfacing | shoulder | ankle | arthrodesis | soft tissue | aka | total femur | makoplasty | acetabulloplasty | bipolar | elbow total
Inclusions	
Procedure text must include	total | tot knee | tot hip | tka | tha

Appendix Table A.3. Overall cardiometabolic comorbidity frequencies by definition type (N = 81,871)

	ICD Code Yes, n (%)	Physiologic/ Laboratory Yes, n (%)	History and Physical Yes, n (%)	Overall Yes, n (%)	ICD 9/10 Definition	Laboratory or Physiologic Definition
Hypertension	53,430 (65.3)	39,886 (48.7)	33,715 (41.2)	65,791 (80.4)	40[2-5], 40[2-5].%, I1[1,2,3,5].%, 401.%, 401, I10, I10.%	Baseline SBP ≥ 140mmHg or baseline DBP ≥ 90mmHg or baseline MAP >107mmHg
High Cholesterol	39,507 (48.3)	7,087 (8.7)	7,770 (9.5)	45,304 (55.3)	272.[0-4], E78.0, E78.[0-4]%, E78.5	Cholesterol ≥ 200mg/dL, or triglyceride ≥ 150mg/dL, or HDL cholesterol ≤ 40mg/dL for men and ≤ 50mg/dL for women, or LDL cholesterol ≥ 100mg/dL
Peripheral Vascular Disorders	4,273 (5.2)	NA	151 (0.2)	4,355 (5.3)	093.0%, 437.3%, 443.[1–9]%, 447.1%, V43.4%, 44[0,1], 44[0,1].%, 557.[1,9]%, I77.1%, Z95.[8,9]%, I73.[1,8,9]%, I79.[0,2]%,K55.[1,8,9]%, I7[0,1].%	N/A
Diabetes	15,637 (19.1)	6,283 (7.7)	5,906 (7.2)	16,925 (20.7)	250.[4-9]%, E1[0-4].[2–8]%, 250.[0-3]%, E1[0-4].[0,1,9]%	HbA1c level ≥ 6.5%
Systemic Inflammatory Disorders	5,570 (6.8)	NA	143 (0.2)	5,593 (6.8)	446, 446.%, 714, 714.%, 719.3%, 701.0%, 72[0,5], 72[0,5].%, 710.[0–4,8,9]%, 711.2%, 728.5%, 728.89, 729.30, M30.%, M31.[0–3]%, M0[5,6,8].%, M12.[0,3]%, L94.[0,1,3]%, M45.%, M46.[1,8,9]%, M3[2-5].%	N/A
Hypothyroidism	13,932 (17.0)	768 (0.9)	911 (1.1)	14,292 (17.5)	24[3,4], 24[3,4].%, 240.9%, 246.[1,8]%, E0[0-3], E0[0-3].%, E89.0%	Thyroid stimulating hormone laboratory level > 4.0 mU/L
Cardiac Arrhythmias	14,421 (17.6)	NA	4,406 (5.4)	15,760 (19.3)	996.0[1,4], 426.[0,7,9]%, 426.1[0,2,3], 427.[0-4,6-9]%, 785.0%, V45.0%, V53.3%, T82.1%, I44[1-3].%, I45.[69]%, I4[7-9], I4[7-9].%, R00.[0,1,8]%, Z45.0%, Z95.0%	N/A
Congestive Heart Failure	4,014 (4.9)	NA	1,421 (1.7)	4,429 (5.4)	425.[4–9]%, 428, 428.%, 404.[0,1,9]3, 40[2,4].[0,1,9]1, 398.91, I43, I43.%, I42.[0,5–9]%, I25.5%, 150, 150.%, I11.0%, I13.[0,2]%, I09.9%, P29.0%	N/A
Coronary Artery Disease	9,861 (12.0)	NA	5,079 (6.2)	10,594 (12.9)	412, 414.2, 414.8, 414.9, V45.81, V45.82, I25.10, I25.110, I25.111, I25.118, I25.119, I25.2, I25.5, I25.6. I25.700, I25.701, I25.708, I25.709, I25.710, I25.711, I25.718, I25.719, I25.720, I25.721, I25.728, I25.729, I25.730, I25.731, I25.738, I25.739,	N/A

					I25.750, I25.751, I25.758, I25.759, I25.760, I25.761, I25.768, I25.769, I25.790, I25.791, I25.798, I25.799, I25.810, I25.811, I25.812, I25.82, I25.83, I25.84, I25.89, I25.9, Z95.1, Z95.5, Z98.61	
Obesity	28,736 (35.1)	41,634 (50.9)	NA	45,214 (55.2)	278.0%, E66.%	Body mass index ≥ 30 kg/m^2

Yes frequency and percentage are presented out of the total analytic sample (N = 81,871 cases). Abbreviations: SBP – systolic blood pressure, DBP – diastolic blood pressure, MAP – mean arterial pressure, HDL - high-density lipoprotein, LDL - low-density lipoproteins

Appendix Table A.4. Demographic characteristics of total knee and hip arthroplasty patients, by derivation and validation datasets

	DERIVATION DATASET			VALIDATION DATASET			
	Overall (N = 55,798)	**No Acute Kidney Injury (N = 53,109)**	**Any Acute Kidney Injury (N = 2,689)**	**Overall (N = 26,073)**	**No Acute Kidney Injury (N = 24,739)**	**Any Acute Kidney Injury (N = 1,334)**	**Absolute Standardized Differences[a]**
Demographics							
Age							0.115
18-29	347 (0.6)	336 (0.6)	11 (0.4)	172 (0.7)	169 (0.7)	3 (0.2)	
30-39	731 (1.3)	715 (1.4)	16 (0.6)	369 (1.4)	364 (1.5)	5 (0.4)	
40-49	2,799 (5.0)	2,709 (5.1)	90 (3.4)	1,522 (5.8)	1,490 (6.0)	32 (2.4)	
50-59	10,659 (19.1)	10,262 (19.3)	397 (14.8)	5,808 (22.3)	5,554 (22.5)	254 (19.0)	
60-69	19,957 (35.8)	19,042 (35.8)	915 (34.0)	9,406 (36.1)	8,912 (36.0)	494 (37.0)	
70-79	15,949 (28.6)	15,082 (28.4)	867 (32.2)	6,821 (26.2)	6,415 (25.9)	406 (30.4)	
80+	5,356 (9.6)	4,963 (9.3)	393 (14.6)	1,975 (7.6)	1,835 (7.4)	140 (10.5)	
BMI	31.2 ± 6.6	31.1 ± 6.6	33.7 ± 7.3	31.7 ± 7.0	31.5 ± 6.9	34.9 ± 8.0	0.075
Gender							0.021
Male	22,511 (40.3)	21,255 (40.0)	1,256 (46.7)	10,247 (39.3)	9,691 (39.2)	556 (41.7)	
Female	33,287 (59.7)	31,854 (60.0)	1,433 (53.3)	15,826 (60.7)	15,048 (60.8)	778 (58.3)	
Race							0.406
Non-Hispanic White	43,696 (78.3)	41,767 (78.6)	1,929 (71.7)	18,192 (69.8)	17,476 (70.6)	716 (53.7)	
Non-Hispanic Black	5,095 (9.1)	4,658 (8.8)	437 (16.3)	5,924 (22.7)	5,380 (21.8)	544 (40.8)	
Hispanic	523 (0.9)	493 (0.9)	30 (1.1)	317 (1.2)	304 (1.2)	13 (1.0)	
Other	6,484 (11.6)	6,191 (11.7)	293 (10.9)	1,640 (6.3)	1,579 (6.4)	61 (4.6)	
ASA Class							0.159
1	1,082 (1.9)	1,073 (2.0)	9 (0.3)	443 (1.7)	437 (1.8)	6 (0.5)	
2	25,414 (45.6)	24,795 (46.7)	619 (23.0)	13,599 (52.2)	13,194 (53.3)	405 (30.4)	
3	27,961 (50.1)	26,133 (49.2)	1,828 (68.0)	11,756 (45.1)	10,879 (44.0)	877 (65.7)	
4	1,341 (2.4)	1,108 (2.1)	233 (8.7)	275 (1.1)	229 (0.9)	46 (3.5)	
Smoking Status							0.399
Current Smoker	3,619 (6.5)	3,402 (6.4)	217 (8.1)	3,925 (15.1)	3,672 (14.8)	253 (19.0)	
Former Smoker	1,584 (2.8)	1,501 (2.8)	83 (3.1)	378 (1.5)	357 (1.4)	21 (1.6)	
Never Smoker	5,257 (9.4)	5,089 (9.6)	168 (6.3)	4,482 (17.2)	4,286 (17.3)	196 (14.7)	
Unknown	45,338 (81.3)	43,117 (81.2)	2,221 (82.6)	17,288 (66.3)	16,424 (66.4)	864 (64.8)	
Cardiometabolic Conditions for Latent Class Analysis							
Hypertension	45,616 (81.8)	43,091 (81.1)	2,525 (93.9)	20,175 (77.4)	18,910 (76.4)	1,265 (94.8)	0.109
High cholesterol	29,773 (53.4)	28,091 (52.9)	1,682 (62.6)	15,531 (59.6)	14,625 (59.1)	906 (67.9)	0.126
Peripheral Vascular Disorders	2,759 (4.9)	2,500 (4.7)	259 (9.6)	1,596 (6.1)	1,429 (5.8)	167 (12.5)	0.052
Diabetes	11,252 (20.2)	10,269 (19.3)	983 (36.6)	5,673 (21.8)	5,167 (20.9)	506 (37.9)	0.039
Systemic Inflammatory Disorders	3,793 (6.8)	3,617 (6.8)	176 (6.6)	1,800 (6.9)	1,704 (6.9)	96 (7.2)	0.004
Hypothyroidism	10,122 (18.1)	9,538 (18.0)	584 (21.7)	4,170 (16.0)	3,932 (15.9)	238 (17.8)	0.057
Cardiac Arrhythmias	10,418 (18.7)	9,642 (18.2)	776 (28.9)	5,342 (20.5)	4,920 (19.9)	422 (31.6)	0.046
Congestive Heart Failure	2,973 (5.3)	2,564 (4.8)	409 (15.2)	1,456 (5.6)	1,230 (5.0)	226 (16.9)	0.011
Coronary Artery Disease	7,267 (13.0)	6,617 (12.5)	650 (24.2)	3,327 (12.8)	3,012 (12.2)	315 (23.6)	0.008

Additional Comorbidities							
Obesity	30,091 (53.9)	28,262 (53.2)	1,829 (68.0)	15,123 (58.0)	14,142 (57.2)	981 (73.5)	0.082
Preoperative Hypotension	8,357 (15.0)	7,705 (14.5)	652 (24.3)	7,990 (30.6)	7,503 (30.3)	487 (36.5)	0.380
Estimated Glomerular Filtration Rate	77.8 ± 22.3	78.2 ± 21.9	68.1 ± 27.8	79.4 ± 22.6	79.9 ± 22.3	70.4 ± 25.6	0.075
Intraoperative Characteristics							
Procedure Type							0.007
Knee	31,740 (56.9)	30,256 (57.0)	1,484 (55.2)	14,922 (57.2)	14,164 (57.3)	758 (56.8)	
Hip	24,058 (43.1)	22,853 (43.0)	1,205 (44.8)	11,151 (42.8)	10,575 (42.8)	576 (43.2)	
Use of General Anesthesia	22,327 (40.0)	20,912 (39.4)	1,415 (52.6)	8,394 (32.2)	7,772 (31.4)	622 (46.6)	0.163
Packed Red Blood Cell Transfusion	390 (0.7)	331 (0.6)	59 (2.2)	141 (0.5)	119 (0.5)	22 (1.7)	0.020
Total Fluid Volume, Crystalloid Equivalents	1,562.0 ± 1,315.1	1,558.3 ± 1,327.2	1,634.8 ± 1,046.5	1,554.0 ± 1,191.8	1,562.1 ± 1,206.1	1,403.8 ± 873.2	0.006
Minutes of MAP <65	3.0 [0.0 to 14.0]	3.0 [0.0 to 14.0]	3.0 [0.0 to 13.0]	3.0 [0.0 to 12.0]	3.0 [0.0 to 12.0]	3.0 [0.0 to 10.0]	0.048
Tranexamic acid use	33,587 (60.2)	32,064 (60.4)	1,523 (56.6)	20,874 (80.1)	20,015 (80.9)	859 (64.4)	0.445
Nephrotoxic Medication Use	48,651 (87.2)	46,241 (87.1)	2,410 (89.6)	24,087 (92.4)	22,892 (92.5)	1,195 (89.6)	0.172
Diuretic	51 (0.1)	44 (0.1)	7 (0.3)	16 (0.1)	13 (0.1)	3 (0.2)	0.011
Antibiotic	48,372 (86.7)	45,981 (86.6)	2,391 (88.9)	23,616 (90.6)	22,446 (90.7)	1,170 (87.7)	0.123
NSAID	3,890 (7.0)	3,702 (7.0)	188 (7.0)	5,679 (21.8)	5,482 (22.2)	197 (14.8)	0.432

Data are presented as either mean ± standard deviation, median [25th to 75th percentile] or frequency (percentage of non-missing data). An absolute standardized difference >0.20 indicates a significant difference for the condition for those with and without AKI.

[a] Comparing overall training dataset to overall testing dataset

Appendix Table A.5. Unadjusted odds ratios for the outcome of acute kidney injury with two different iterations of derivation and validation datasets

		Actual Derivation/Validation Split		Sensitivity 50/50 Within Institution Split	
		Derivation Dataset	**Validation Dataset**	**Derivation Dataset**	**Validation Dataset**
3-Class Model					
MetS		1.86 (1.70, 2.04)	2.20 (1.92, 2.52)	1.97 (1.77, 2.20)	1.95 (1.76, 2.17)
Hypertension Only		Reference	Reference	Reference	Reference
MetS and CVD		4.38 (3.92, 4.89)	4.93 (4.20, 5.79)	4.39 (3.85, 5.01)	4.70 (4.14, 5.34)
3-Class Model Interaction with Obesity Status					
MetS	Non-obese	1.64 (1.40, 1.92)	2.19 (1.70, 2.81)	2.02 (1.67, 2.44)	1.59 (1.32, 1.91)
	Obese	3.12 (2.73, 3.56)	4.06 (3.28, 5.02)	3.55 (3.02, 4.19)	3.22 (2.76, 3.75)
Hypertension Only	Non-obese	Reference	Reference	Reference	Reference
	Obese	1.79 (1.54, 2.07)	2.08 (1.64, 2.65)	2.07 (1.73, 2.49)	1.68 (1.41, 2.00)
MetS and CVD	Non-Obese	5.04 (4.21, 6.05)	5.27 (3.93, 7.06)	5.19 (4.15, 6.50)	5.00 (4.04, 6.17)
	Obese	6.61 (5.66, 7.72)	9.05 (7.13, 11.48)	7.56 (6.26, 9.14)	7.04 5.89, 8.41)

Unadjusted odds ratios were computed using a bivariate logistic regression for the outcome of interest of AKI status. Abbreviations: MetS – metabolic syndrome, CVD – cardiovascular disease, CAD – coronary artery disease

Appendix Table A.6. Frequency and odds of acute kidney injury by 3-class latent class grouping

		Overall (N = 81,871)	**No Acute Kidney Injury (N = 77,848)**	**Any Acute Kidney Injury (N = 4,023)**	**Absolute Standardized Differences**	**Unadjusted Odds Ratios (95% CI)**
3-Class Model					0.508	
	Hypertension Only	37,032 (45.2)	35,970 (46.2)	1,062 (26.4)		Reference
	MetS	36,889 (45.1)	34,869 (44.8)	2,020 (50.2)		1.96 (1.82, 2.12)
	MetS and CVD	7,950 (9.7)	7,009 (9.0)	941 (23.4)		4.55 (4.15, 4.98)
3-Class Model Interaction with Obesity Status					0.585	
Hypertension Only	Non-obese	19,468 (23.8)	19,067 (24.5)	401 (10.0)		Reference
	Obese	17,564 (21.5)	16,903 (21.7)	661 (16.4)		1.86 (1.64, 2.11)
MetS	Non-obese	14,030 (17.1)	13,523 (17.4)	507 (12.6)		1.78 (1.56, 2.04)
	Obese	22,859 (27.9)	21,346 (27.4)	1,513 (37.6)		3.37 (3.01, 3.77)
MetS + CVD	Non-obese	3,159 (3.9)	2,854 (3.7)	305 (7.6)		5.08 (4.36, 5.93)
	Obese	4,791 (5.9)	4,155 (5.3)	636 (15.8)		7.28 6.40, 8.28)

Abbreviations: MetS – metabolic syndrome, CVD – cardiovascular disease, CAD – coronary artery disease

Appendix Table A.7. Unadjusted odds of AKI for those with obesity compared to those without, within each latent class

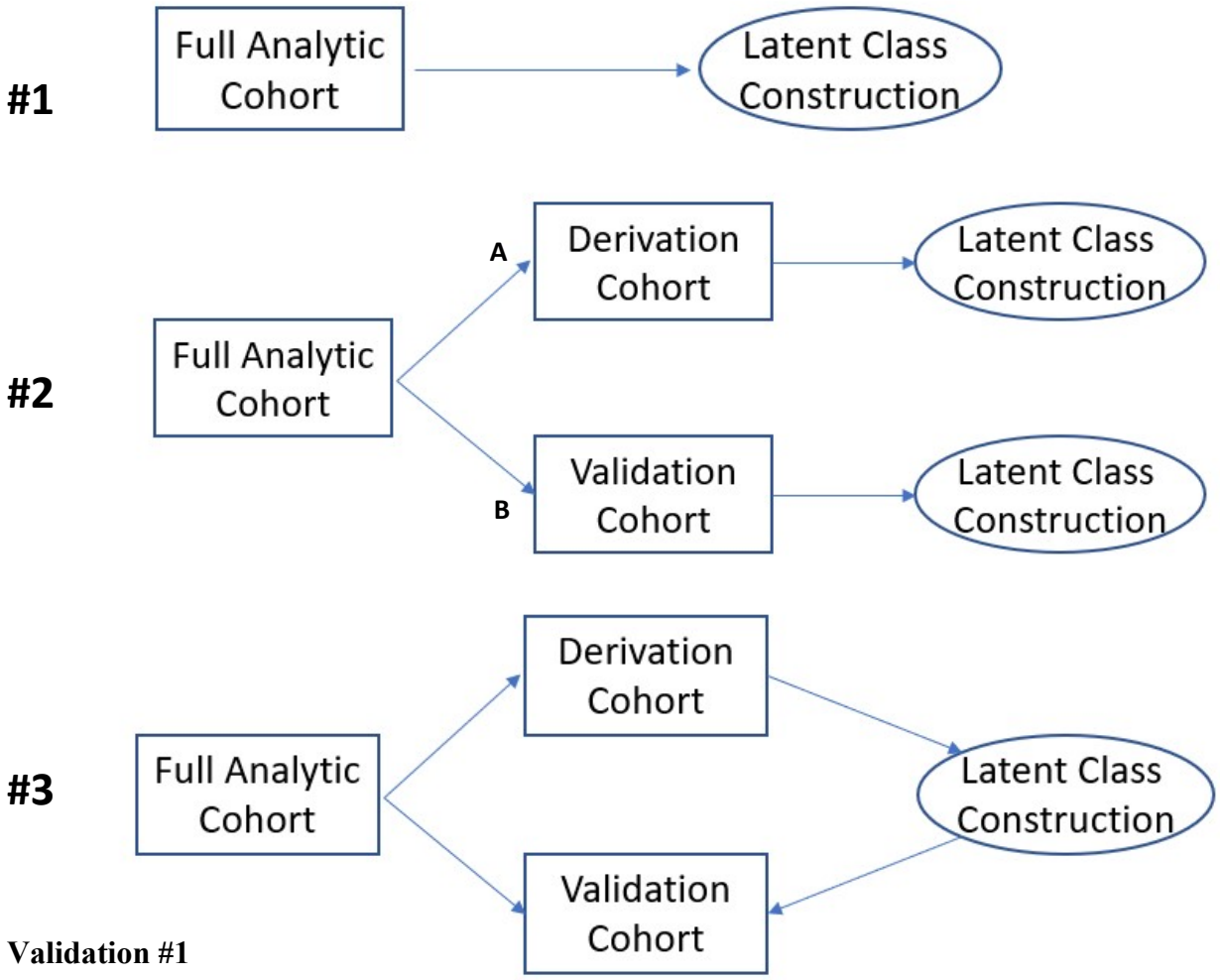
	Derivation Dataset (N = 55,798)	**Validation Dataset (N = 26,073)**
MetS	1.90 (1.68, 2.15)	1.86 (1.55, 2.22)
Hypertension Only	1.79 (1.54, 2.07)	2.08 (1.64, 2.65)
MetS and CVD	1.31 (1.10, 1.56)	1.72 1.33, 2.22)

Unadjusted odds ratios were computed using a bivariate logistic regression for the outcome of interest of AKI status. Abbreviations: MetS – metabolic syndrome, CVD – cardiovascular disease, CAD – coronary artery disease

Appendix B

Sensitivity Analyses for Latent Class Analysis

Visualizations of latent class analyses validations conducted



Validation #1

Examining posterior probability of class membership for assigned classes within full dataset.

Appendix Table B.1 shows the posterior probability of class membership for the assigned latent class, as computed from the full data cohort LCA construction. As you can see, membership within an assigned class was generally associated with a high predicted probability of membership within the given class. Across the full cohort, 7.8% of those in the MetS group had <50% probability of class membership in the given class, 0.3% of those in the Hypertension Only group had <50% probability of class membership in the given class, and 2.3% of those in the MetS+CVD group had <50% probability of class membership in that class.

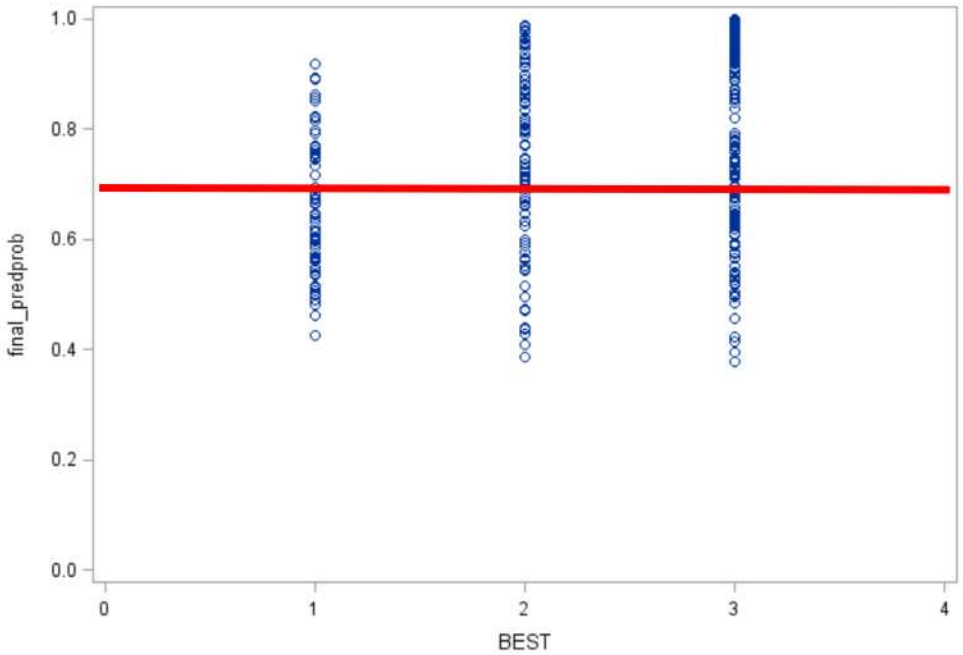
Appendix Figure B.1 shows the distribution of predicted probability of class membership for the assigned class. Appendix Figures 2.2.2-2.2.4 show the full probability distributions for everyone assigned to the HTN Only group (Appendix Figure B.2), the MetS group (Appendix Figure B.3), and the MetS+CVD group (Appendix Figure B.4).

Appendix Table B.1. Summary statistics of posterior class membership probability for assigned class, validation #1

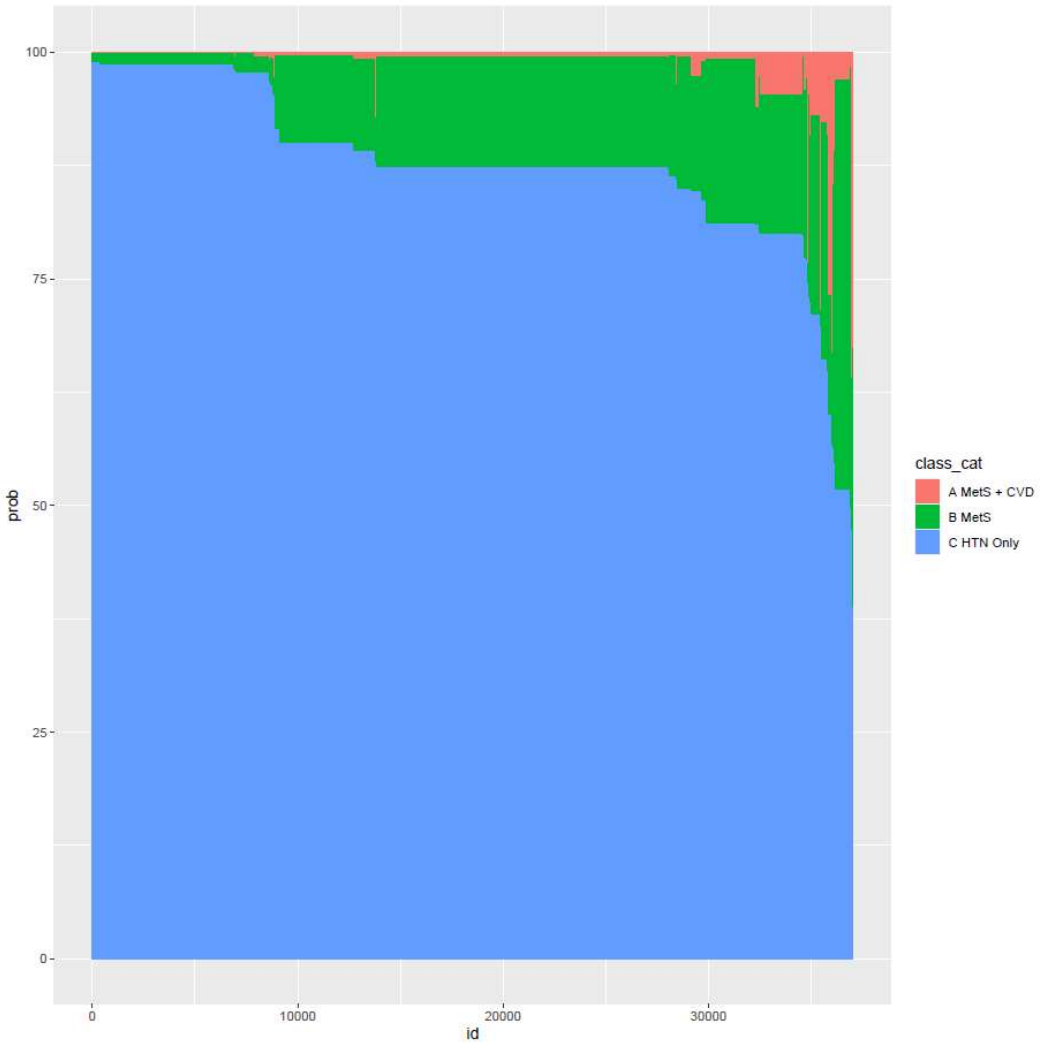
	Mean	StDev	Min	Max
MetS	0.6393	0.1513	0.4253	0.9182
HTN Only	0.8762	0.0919	0.3876	0.9879
MetS + CVD	0.7938	0.1629	0.3793	0.9994

Abbreviations: MetS – metabolic syndrome, HTN – hypertension, CVD – cardiovascular disease

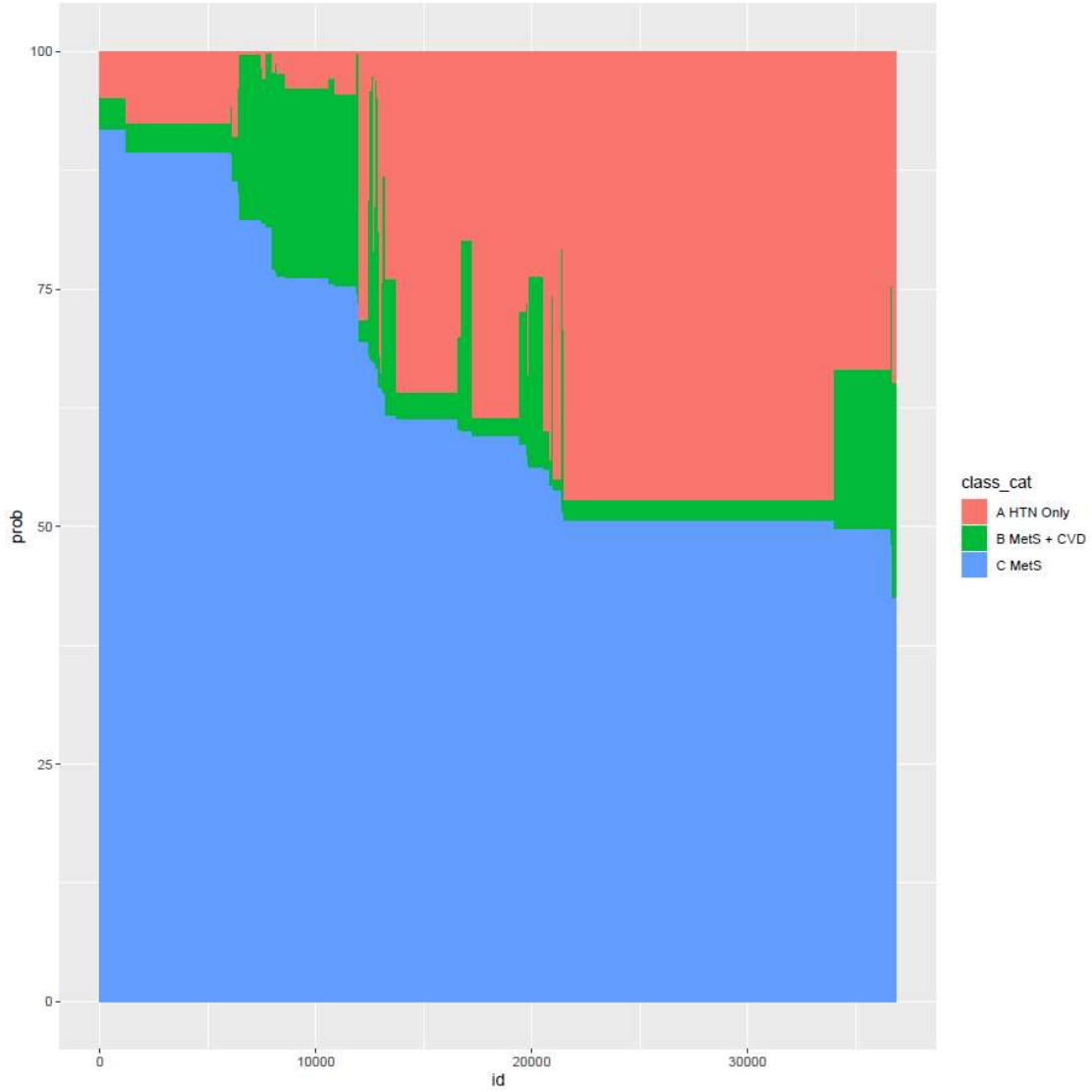
Of the 36,889 people assigned MetS, 2873 (7.8%) had <50% probability of class membership
Of the 37,032 people assigned HTN Only, 106 (0.3%) had <50% probability of class membership
Of the 7,950 people assigned MetS + CVD, 181 (2.3%) had <50% probability of class membership



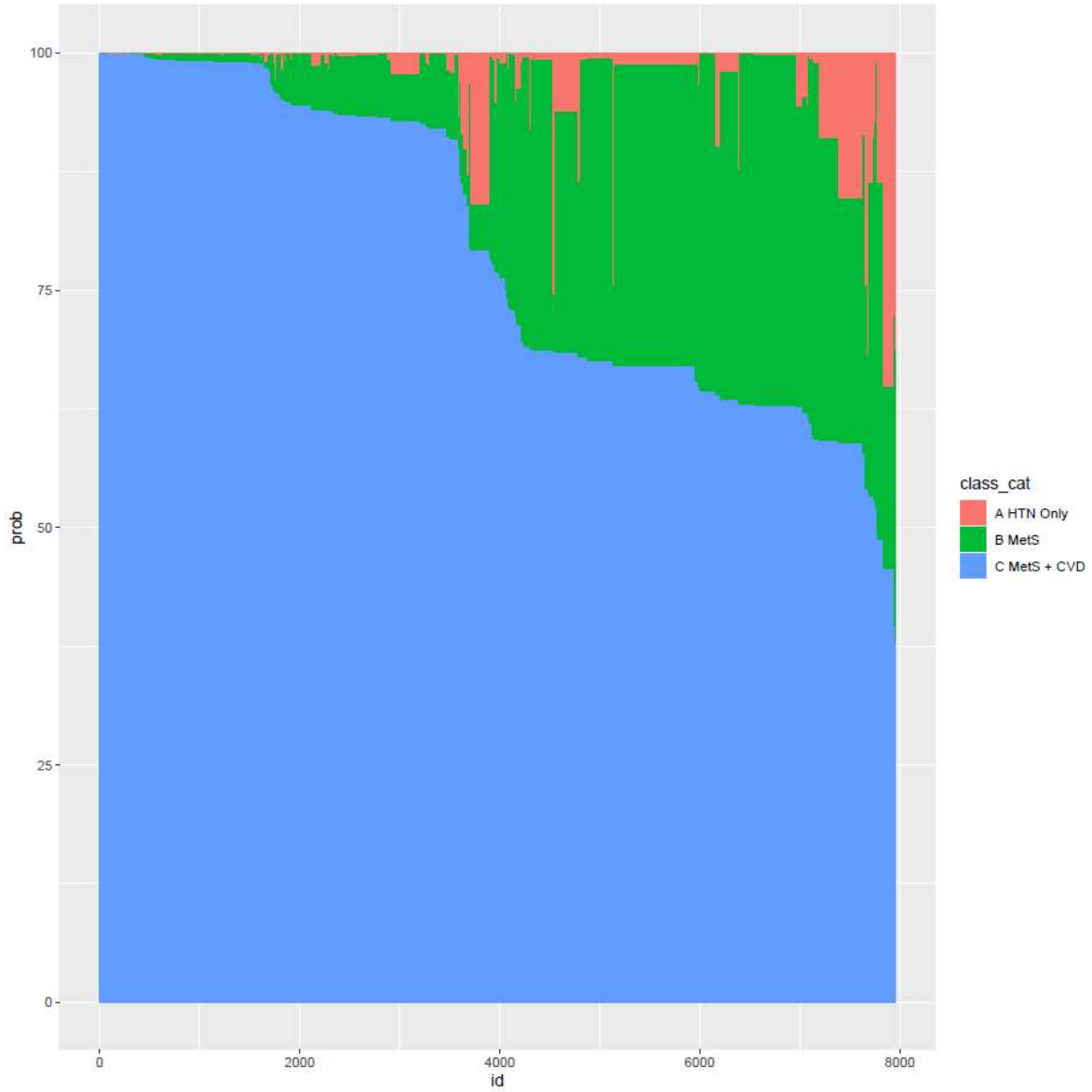
Appendix Figure B.1. Predicted probability of class membership for the assigned class. 1 = "MetS", 2 = "HTN Only", 3 = "MetS + CVD"



Appendix Figure B.2. Stacked bar chart of individual-level predicted probabilities of class membership for those assigned to the "HTN Only" class.



Appendix Figure B.3. Stacked bar chart of individual-level predicted probabilities of class membership for those assigned to the "MetS" class.



Appendix Figure B.4. Stacked bar chart of individual-level predicted probabilities of class membership for those assigned to the "MetS + CVD" class.

Validation #2A

Latent class construction was run again for the 3-class model within only those in the derivation cohort. Posterior probability of class membership was then compared with that from the latent classes constructed within the full analytic cohort.

Appendix Table B.2 below shows the posterior probability of class membership for the assigned latent class, as computed from a new LCA model constructed only within the derivation cohort. Similar classes emerged to the full cohort, as would be expected given the derivation cohort makes up a significant portion of the full analytic cohort (Appendix Figure B.5). As you can see, membership within an assigned class was generally associated with a high predicted probability of membership within the given class (Appendix Figure B.6, Appendix Table B.2). Across the full cohort, 1.1% of those in the MetS group had <50% probability of class membership in the given class, 0.2% of those in the Hypertension Only group had <50% probability of class membership in the given class, and 1.4% of those in the MetS+CVD group had <50% probability of class membership in that class.

Appendix Table B.3 shows high agreement of LCA models constructed in the derivation cohort with those classes constructed in the full cohort. Appendix Figure B.7 depicts a scatterplot matrix of predicted probability based on class membership, showing strong agreement and linearity between classes assigned in the full cohort versus those from the derivation only cohort.

Appendix Table B.2. Summary statistics of posterior class membership probability for assigned class, validation #2A

	Mean	StDev	Min	Max
MetS	0.6637	0.1339	0.3869	0.9214
HTN Only	0.8796	0.0764	0.3832	0.9871
MetS + CVD	0.8013	0.1624	0.3643	0.9995

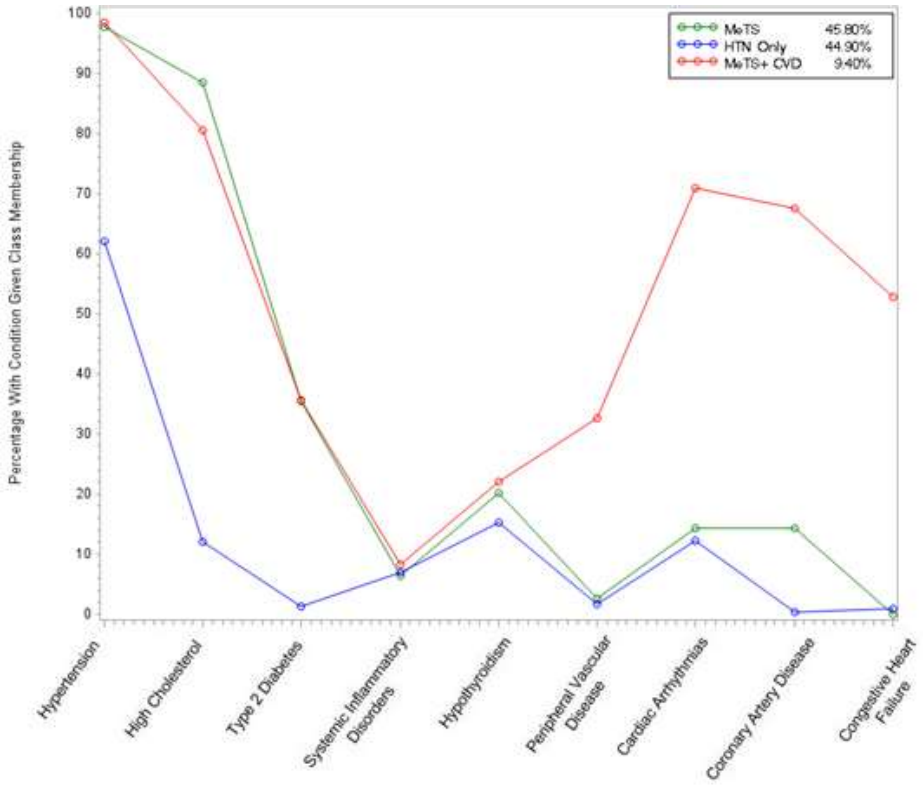
Abbreviations: MetS – metabolic syndrome, HTN – hypertension, CVD – cardiovascular disease

Of the 25530 people assigned MetS, 293 (1.1%) had <50% probability of class membership
Of the 25049 people assigned HTN Only, 55 (0.2%) had <50% probability of class membership
Of the 5219 people assigned MetS + CVD, 72 (1.4%) had <50% probability of class membership

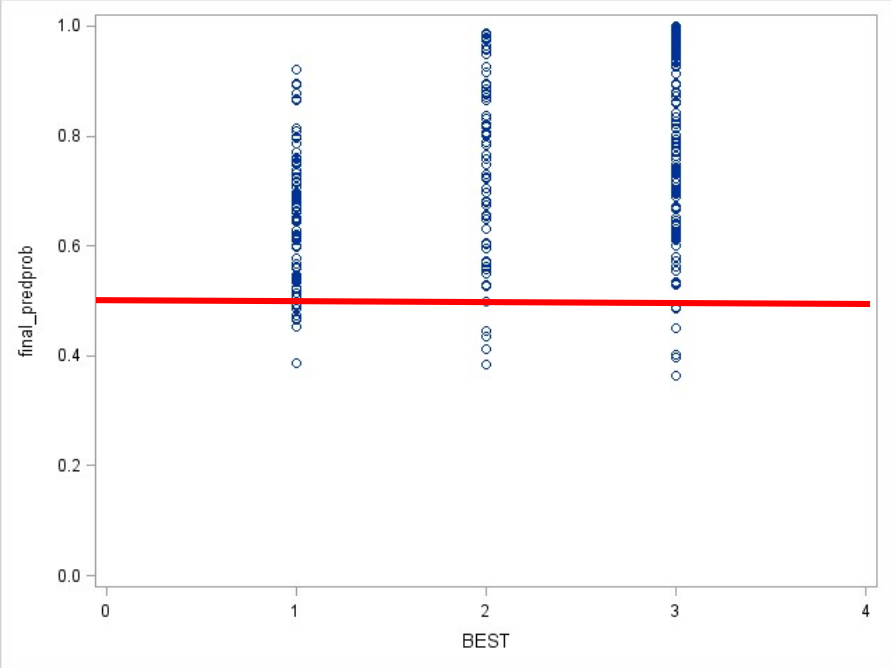
Appendix Table B.3. Crosstabs comparing derivation cohort latent class assignments (rows) to original cohort latent class assignments (columns)

		Original (Full) Cohort		
		MetS	**HTN Only**	**MetS + CVD**
Derivation Cohort	**MetS**	24945 (100.0)	525 (2.1)	60 (1.1)
	HTN Only	0 (0.0)	25049 (97.9)	0 (0.0)
	MetS + CVD	0 (0.0)	1 (0.0)	5218 (98.9)

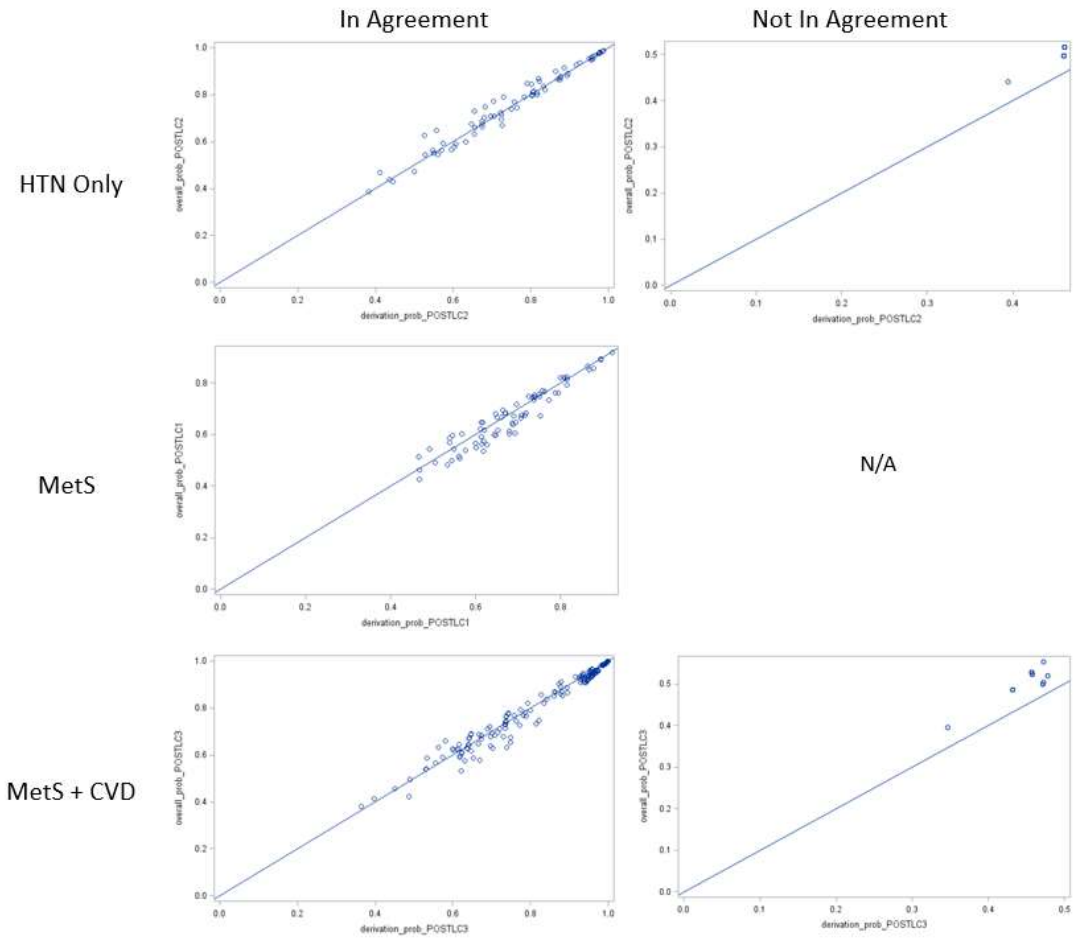
Data are presented as n (column %). Abbreviations: MetS – metabolic syndrome, HTN – hypertension, CVD – cardiovascular disease



Appendix Figure B.5. Percentage of cases with a cardiometabolic condition given class membership for the three-class latent class model when derived in the derivation cohort.



Appendix Figure B.6. Predicted probability of class membership for the assigned class – derivation only cohort. 1 = "MetS", 2 = "HTN Only", 3 = "MetS + CVD″



Appendix Figure B.7. Scatterplot of predicted probability of class membership for those who were assigned the specified class within the full analytic cohort. The y-axis represents the predicted probability of class membership for the full analytic cohort, and the x-axis represents the predicted probability of class membership for the derivation cohort derived latent class. Those data points represented in the "In Agreement" column are those individuals who were assigned the same class when latent classes were constructed in the full analytic cohort and in the derivation cohort. Those in the "Not In Agreement" column are those individuals who were not assigned the same classes between latent class constructions. Abbreviations: MetS – metabolic syndrome, HTN – hypertension, CVD – cardiovascular disease

Validation #2B

Latent class construction was run again for the 3-class model within only those in the validation cohort. Posterior probability of class membership was then compared with that from the latent classes constructed within the full analytic cohort.

Appendix Table B.4 below shows the posterior probability of class membership for the assigned latent class, as computed from a new LCA model constructed only within the validation cohort. Similar classes emerged to the full cohort, though there were significantly more individuals in the HTN only group and fewer in the MetS group than the derivation only and full analytic cohort LCA class groupings (Appendix Figure B.8). Membership within an assigned class was generally associated with a high predicted probability of membership within the given class (Appendix Figure B.9, Appendix Table B.4). Across the full cohort, 16.2% of those in the MetS group had <50% probability of class membership in the given class, 2.4% of those in the Hypertension Only group had <50% probability of class membership in the given class, and 1.7% of those in the MetS + CVD group had <50% probability of class membership in that class.

Appendix Table B.5 shows high agreement of LCA models constructed in the validation cohort with those classes constructed in the full cohort for those in the HTN only group and those in the MetS + CVD group. Appendix Figure B.10 depicts a scatterplot matrix of predicted probability based on class membership, showing strong agreement and linearity between classes assigned in the full cohort versus those from the validation only cohort. There is a significant amount of heterogeneity of class assignment for those in the MetS group in the original cohort, with 37% being assigned HTN only in the validation LCA model. Appendix Tables B.6-B.9 highlight characteristics of these individuals. Those who were assigned the MetS class in the full cohort and HTN only in the

validation cohort LCA models had significant proportions of hypertension and high cholesterol (>94% for both), and minimal additional cardiometabolic comorbidity. These individuals additionally had a mean predicted probability of class membership straddling 50% for both the full cohort and validation cohort LCA models.

Appendix Table B.4. Checking posterior class membership probability for assigned class, validation #2B

	Mean	StDev	Min	Max
MetS	0.7004	0.1697	0.4030	0.9159
HTN Only	0.7840	0.1748	0.3967	0.9887
MetS + CVD	0.8135	0.1507	0.4103	0.9994

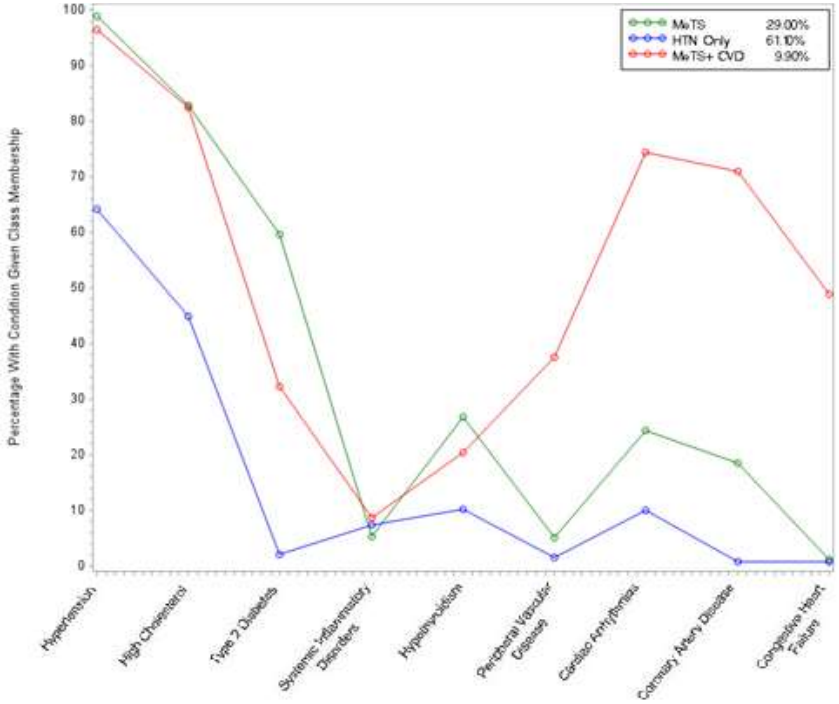
Abbreviations: MetS – metabolic syndrome, HTN – hypertension, CVD – cardiovascular disease

Of the 7557 people assigned MetS, 1228 (16.2%) had <50% probability of class membership
Of the 15926 people assigned HTN Only, 387 (2.4%) had <50% probability of class membership
Of the 2590 people assigned MetS + CVD, 44 (1.7%) had <50% probability of class membership

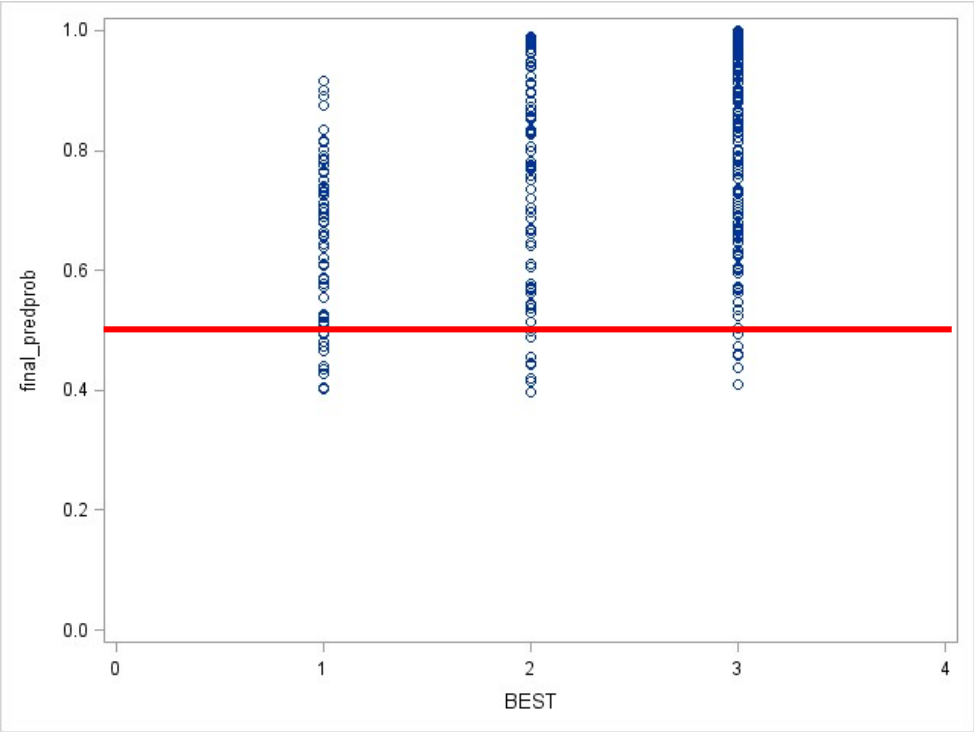
Appendix Table B.5. Crosstabs comparing validation cohort latent class assignments (rows) to original cohort latent class assignments (columns)

		Original (Full) Cohort		
		MetS	HTN Only	MetS + CVD
Validation Cohort	MetS	7473 (62.6)	0 (0.0)	84 (3.1)
	HTN Only	4469 (37.4)	11454 (99.9)	3 (0.1)
	MetS + CVD	2 (0.0)	3 (0.0)	2585 (96.7)

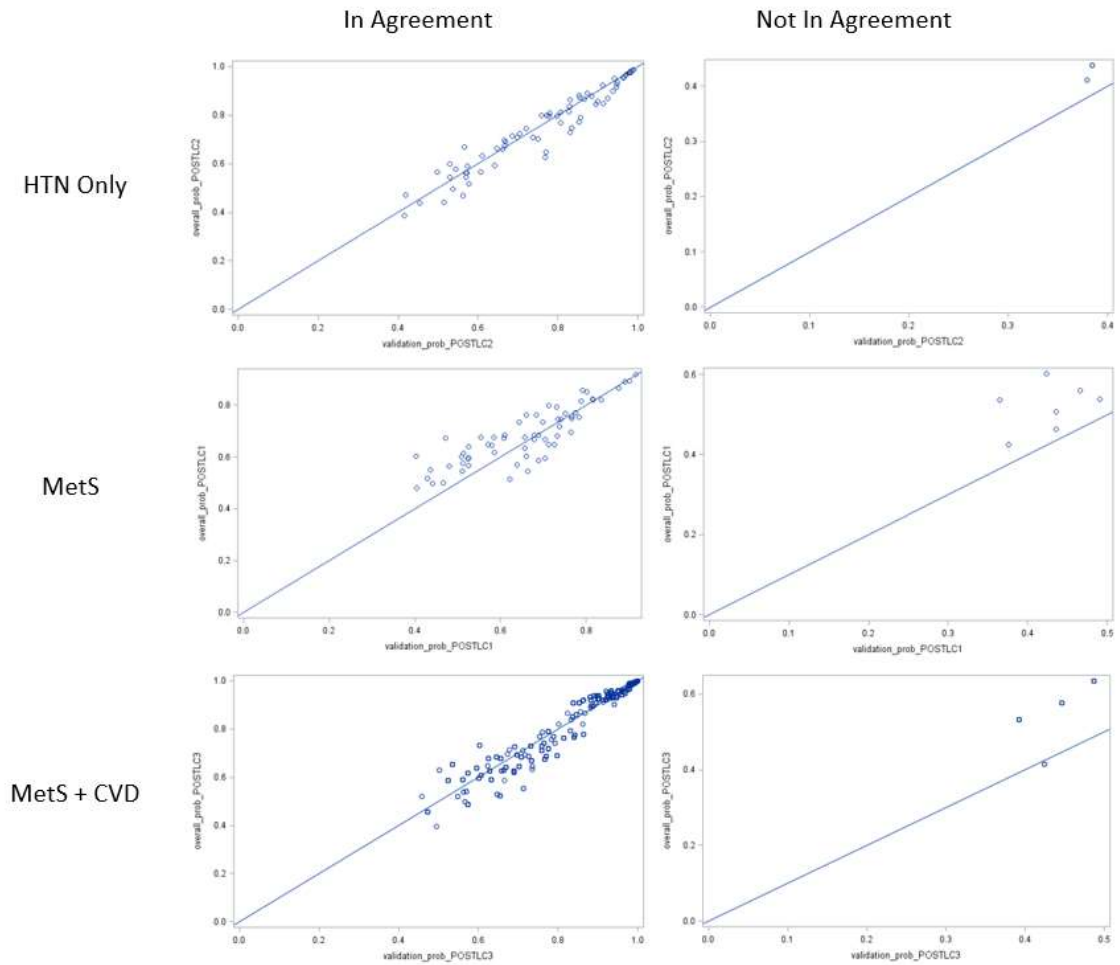
Data are presented as n (column %). Abbreviations: MetS – metabolic syndrome, HTN – hypertension, CVD – cardiovascular disease



Appendix Figure B.8. Percentage of cases with a cardiometabolic condition given class membership for the three-class latent class model when derived in the validation cohort



Appendix Figure B.9. Predicted probability of class membership for the assigned class – validation only cohort. 1 = “MetS”, 2 = “HTN Only”, 3 = “MetS + CVD”



Appendix Figure B.10. Scatterplot of predicted probability of class membership for those who were assigned the specified class within the full analytic cohort. The y-axis represents the predicted probability of class membership for the full analytic cohort, and the x-axis represents the predicted probability of class membership for the validation cohort derived latent class. Those data points represented in the "In Agreement" column are those individuals who were assigned the same class when latent classes were constructed in the full analytic cohort and in the validation cohort. Those in the "Not In Agreement" column are those individuals who were not assigned the same classes between latent class constructions. Abbreviations: MetS – metabolic syndrome, HTN – hypertension, CVD – cardiovascular disease

Appendix Table B.6. Cardiometabolic comorbidity distribution of those MetS in the original cohort and HTN only in the validation cohort

Cardiometabolic Comorbidity	Frequency (%)
Hypertension	4228 (94.6)
High Cholesterol	4469 (100.0)
Peripheral Vascular Disease	0 (0.0)
Diabetes	175 (3.9)
Systemic Inflammatory Disorders	127 (2.8)
Hypothyroid	59 (1.3)
Cardiac Arrhythmia	65 (1.5)
Coronary Artery Disease	66 (1.5)
Congestive Heart Failure	0 (0.0)

Appendix Table B.7. Probability distribution for these individuals from the full cohort who were in the MetS in the original cohort and HTN only in the validation cohort

	Mean	StDev	Min	Max
Overall Cohort (MetS)	0.5084	0.0173	0.4253	0.6019
Validation Cohort (HTN Only)	0.5366	0.0229	0.3967	0.5426

Appendix Table B.8. Cardiometabolic comorbidity distribution of those MetS in the original cohort and MetS in the validation cohort

Cardiometabolic Comorbidity	Frequency (%)
Hypertension	7384 (98.8)
High Cholesterol	6201 (83.0)
Peripheral Vascular Disease	386 (5.2)
Diabetes	4419 (59.1)
Systemic Inflammatory Disorders	390 (5.2)
Hypothyroid	2021 (27.0)
Cardiac Arrhythmia	1843 (24.7)
Coronary Artery Disease	1389 (18.6)
Congestive Heart Failure	0 (0.0)

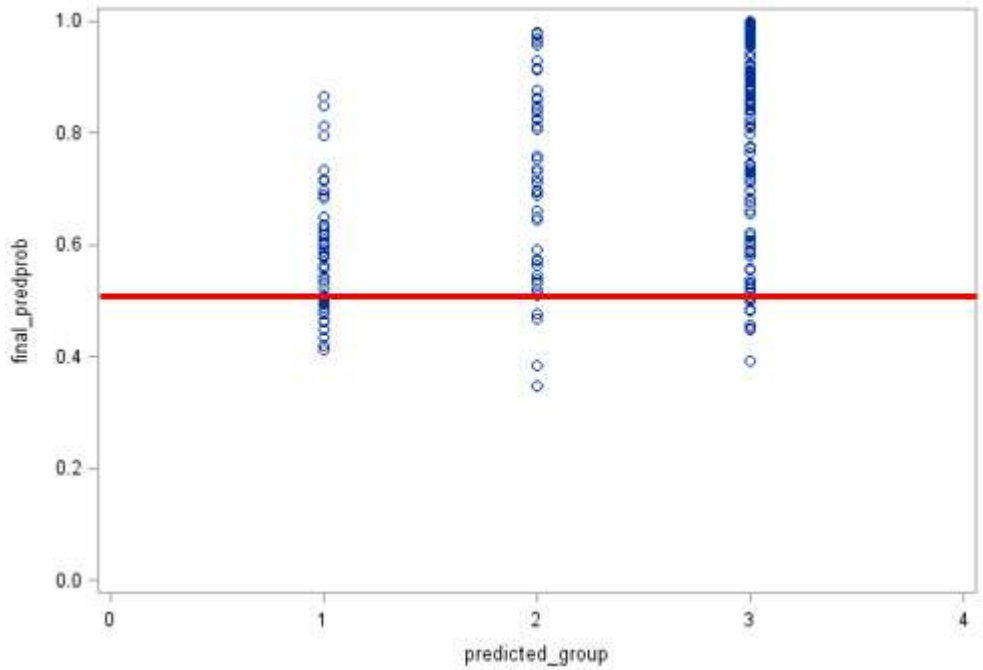
Appendix Table B.9. Probability distribution for these individuals MetS in the original cohort and MetS in the validation cohort

	Mean	StDev	Min	Max
Overall Cohort (MetS)	0.7181	0.1446	0.4808	0.9182
Validation Cohort (MetS)	0.7026	0.1694	0.4030	0.9159

Validation #3

Latent class construction was run for the 3-class model within only those in the derivation cohort. Model coefficients were then hand-coded into those in the validation cohort, and the latent class with the highest posterior predicted value was assigned for class membership. Posterior probability of class membership was then compared with that from the latent classes constructed within the full analytic cohort.

There were generally high predicted probabilities of class membership when the coefficients from the derivation only LCA model were applied to the validation cohort (Appendix Table B.10, Appendix Figure B.11). Appendix Figure B.12 depicts a scatterplot matrix of predicted probability based on class membership, showing modestly strong agreement between classes assigned in the full cohort versus those from the derivation-derived model implemented in the validation only cohort. The MetS class had the lowest mean predicted probability, with 10.9% of individuals having <50% probability of class membership. Those assigned MetS with <50% probability of class membership had high prevalence of hypertension, high cholesterol, and cardiac arrhythmias, with lower rates of other cardiometabolic conditions (Appendix Table B.11); this presentation is more characteristic of the MetS + CVD class. Indeed, these individuals had almost identical predicted probability of class membership for MetS and MetS + CVD classes (Appendix Table B.12).



Appendix Figure B.11. Predicted probability of class membership for the assigned class – derivation cohort coefficients coded into validation cohort data. 1 = "MetS", 2 = "HTN Only", 3 = "MetS + CVD"

Appendix Table B.10. Checking posterior class membership probability for assigned class, validation #3

	Mean	StDev	Min	Max
MetS	0.6276	0.1244	0.4109	0.8655
HTN Only	0.8290	0.1093	0.3472	0.9809
MetS + CVD	0.8480	0.1688	0.3937	0.9998

Abbreviations: MetS – metabolic syndrome, HTN – hypertension, CVD – cardiovascular disease

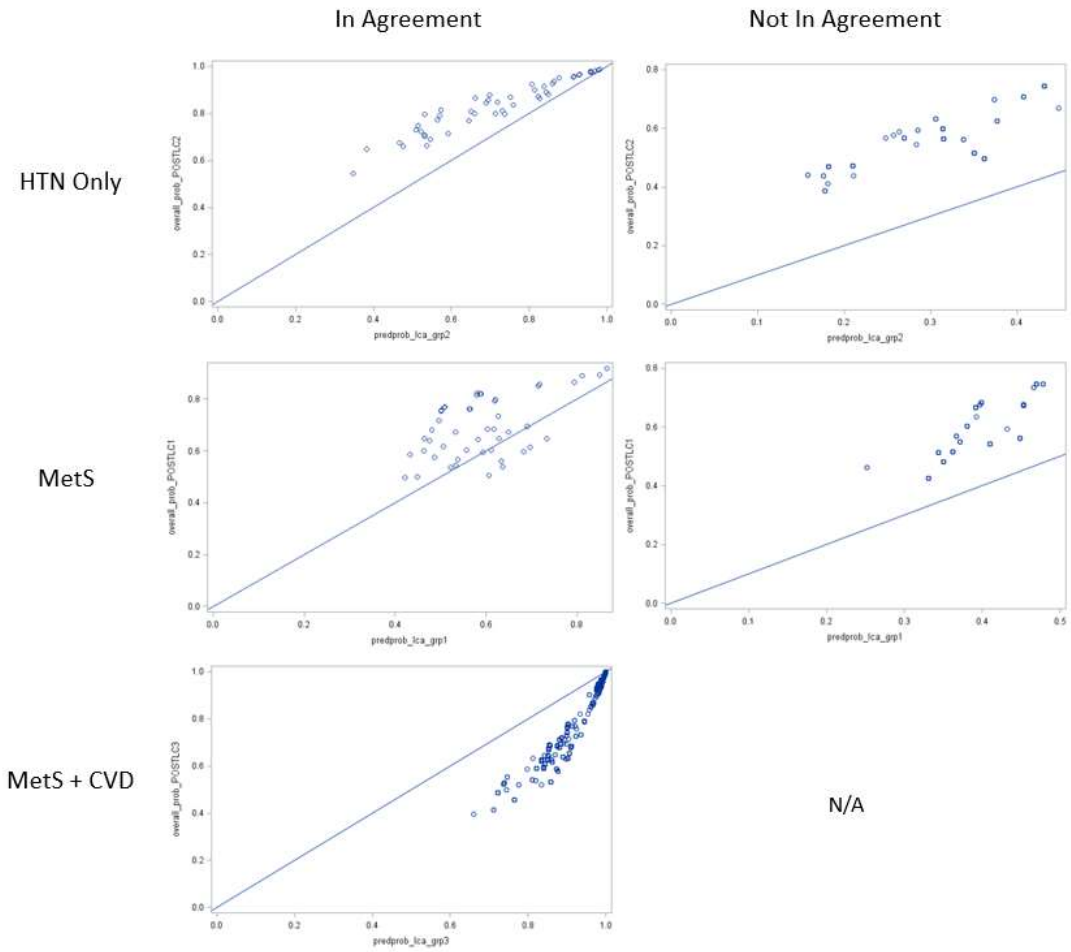
Of the 11,752 people assigned MetS, 1,286 (10.9%) had <50% probability of class membership
Of the 11,049 people assigned HTN Only, 129 (1.2%) had <50% probability of class membership
Of the 3,272 people assigned MetS + CVD, 235 (7.2%) had <50% probability of class membership

Appendix Table B.11. Cardiometabolic comorbidity distribution of those assigned MetS with <50% probability of class membership

Cardiometabolic Comorbidity	Frequency (%)
Hypertension	1277 (99.3)
High Cholesterol	1119 (87.0)
Peripheral Vascular Disease	239 (18.6)
Diabetes	172 (13.4)
Systemic Inflammatory Disorders	5 (0.4)
Hypothyroid	68 (5.3)
Cardiac Arrhythmia	1047 (81.4)
Coronary Artery Disease	0 (0.0)
Congestive Heart Failure	0 (0.0)

Appendix Table B.12. Posterior probability of class membership for those assigned MetS class with <50% probability of class membership

	Mean	StDev	Min	Max
MetS	0.4318	0.0183	0.4109	0.4972
HTN Only	0.1468	0.0368	0.0495	0.3773
MetS + CVD	0.4214	0.0227	0.2118	0.4742



Appendix Figure B.12. Scatterplot of predicted probability of class membership for those who were assigned the specified class within the full analytic cohort. The y-axis represents the predicted probability of class membership for the full analytic cohort, and the x-axis represents the predicted probability of class membership for the derivation-derived latent classes implemented within the validation cohort. Those data points represented in the "In Agreement" column are those individuals who were assigned the same class when latent classes were constructed in the full analytic cohort and in the validation cohort. Those in the "Not In Agreement" column are those individuals who were not assigned the same classes between latent class constructions. Abbreviations: MetS – metabolic syndrome, HTN – hypertension, CVD – cardiovascular disease

Chapter 3

The Relationship Between Comorbid Cardiometabolic Conditions and Acute Kidney Injury is Not Mediated by Intraoperative Factors in Total Joint Arthroplasty

3.1. Abstract

Introduction: Total joint arthroplasty is the most common elective surgery performed in the United States, and those with conditions such as obesity are at higher risk of complications such as postoperative acute kidney injury (AKI). The aim of this study was to determine to what extent the deleterious effects of cardiometabolic diseases on postoperative AKI was mediated by modifiable intraoperative factors.

Methods: This retrospective analysis examined patients ≥18 years of age undergoing primary non-emergent total knee or hip arthroplasties across academic and community health systems within the Multicenter Perioperative Outcomes Group between 2008 and 2019. AKI was defined based upon postoperative creatinine values using modified KDIGO criteria. The primary outcome was any AKI stage ≥1. Cardiometabolic diseases were defined using ICD 9/10 codes, preoperative vital signs and labs, and preoperative history and physical data. Latent classes were constructed from cardiometabolic diseases including hypertension, diabetes, and coronary artery disease. Causal mediation analysis was conducted for the association of latent class and obesity on AKI, with the potential mediators of general anesthesia use and minutes of intraoperative hypotension.

Results: There was no statistically significant interaction between exposures of interest and the mediator of general anesthesia. There were very small statistically significant but not clinically meaningful indirect effects of exposure level through general anesthesia use on AKI, with a range in risk difference of -0.04

per 100 cases (95%CI: -0.05, -0.02; “MetS”/Non-obese compared to “HTN Only”/Non-obese) to 0.14 per 100 cases (95%CI: 0.09, 0.19; “MetS+CVD”/Obese compared to “HTN Only”/Non-obese). There was a statistically significant interaction between the exposure of obesity and the mediator of >12 minutes of intraoperative hypotension, and between the exposure of cardiometabolic latent class/obesity group and the mediator. Similar to the mediator of general anesthesia, there were very small statistically significant but not clinically meaningful indirect effects of exposure level through >12 minutes of intraoperative hypotension on AKI, with a range in risk difference of -0.03 per 100 cases (95%CI: -0.06, -0.01; “HTN Only”/Obese compared to “HTN Only”/Non-obese) to -0.01 per 100 cases (95%CI: -0.03, -0.00; ”MetS” compared to “HTN Only”).

Conclusion: In this multicenter cohort of total knee and hip arthroplasty patients, we found little evidence of a clinically significant mediation effect of general anesthesia use or intraoperative hypotension on the relationship between cardiometabolic comorbidity and postoperative acute kidney injury. Consideration of postoperative monitoring for those at high cardiometabolic risk for AKI should therefore be taken into account regardless of anesthetic protocol when considering where to perform these elective procedures.

3.2 Background

Acute kidney injury (AKI) is a major postoperative complication following cardiac and non-cardiac surgeries, and is associated with increased length of hospital stay, chronic kidney disease, and postoperative mortality[14,84,85]. Although the highest rate of postoperative AKI occurs in the cardiac surgery population (more than 15% of cases), thoracic, vascular, urologic, general, and orthopedic surgeries all have AKI incidence rates greater than 5%[18]. Elective knee and hip total arthroplasty is the most common elective surgery performed in the United States[102,103], and this complication occurs in approximately 2-8% of patients undergoing this surgery[126].

Given the severity and poor outcomes associated with AKI, research has sought to understand predictors and mechanisms of postoperative AKI. Male sex, and conditions including diabetes, hypertension, and pre-existing kidney disease have been shown to significantly increase the risk of AKI. This risk associated with cardiometabolic disease may be due, in part, to higher levels of systemic inflammation or vascular damage which makes the kidneys less resilient to stressors within the operative setting[84,87,88]. Intraoperative factors, including anesthetic type and changes in blood pressure, are also associated with increased risk of AKI[14,21,97,98]. In a non-cardiac cohort, use of general anesthesia was associated with 1.5-2.5 increased odds of AKI compared to neuraxial anesthesia[123,127] and intraoperative hypotension[14] also increased the odds of AKI. In an effort to reduce risk of AKI, anesthesiologists may alter the perioperative treatment in these patients, such as substituting non-nephrotoxic medications when possible. Therefore, the intraoperative window represents a possible opportunity to reduce the risk of procedure-related AKI.

There is a dearth of information available on whether the association between cardiometabolic disease and AKI is due to, or independent of intraoperative factors. This knowledge is needed to inform how to reduce risk in these patients. Thus, the aim of this study was to determine to what extent the deleterious effects of cardiometabolic diseases on postoperative AKI was mediated by modifiable intraoperative factors.

3.3. Methods

The cohort consisted of patients ≥18 years of age presenting to a Multicenter Perioperative Outcomes Group (MPOG) participating hospital for primary non-emergent total knee or hip arthroplasty (anesthesia CPT codes 01402 and 01214, respectively) from January 1, 2008 to December 31, 2019 and who met the MPOG Perioperative Research Standard criteria (Appendix Table C.1). A total of 81,871 cases met final inclusion criteria and represent the analytic sample. This study was approved by the Institutional Review Board at our institution (HUM00180603).

Primary Outcome – Acute Kidney Injury

Acute kidney injury (AKI) was defined by the MPOG phenotype "Complication – Acute Kidney Injury". This criterion was adapted from the validated Kidney Disease – Improving Global Outcomes (KDIGO) definition, which is the globally accepted standard for defining acute kidney injury[14,116] The MPOG definition utilizes the highest postoperative creatinine within 7 days of the recorded anesthesia end time, and the most recent creatinine prior to anesthesia start time. Valid creatinine values must fall between 0.2 mg/dL and 25 mg/dL, inclusive. If the postoperative creatinine within 7 days was ≥ 1.5 times the baseline creatinine or the postoperative creatinine within 48 hours of anesthesia end was ≥ 0.3 mg/dL greater than the baseline creatinine, then AKI stage =1. If the postoperative creatinine within 7 days is ≥ 2 times the baseline value, then the AKI stage =2. If the postoperative creatinine within 7 days is ≥ 3 times the baseline value or if the postoperative value is > 4 mg/dL, then the AKI stage =3. Any other case with valid creatinine values is determined to not have AKI[116]. For the purposes of this study, the outcome of AKI is defined as any KDIGO AKI stage ≥1[14].

Exposures of Interest

The primary exposures of interest are comorbid cardiometabolic disease patterns, obesity, and their interaction. Comorbid cardiometabolic disease patterns were operationalized using latent class analysis to determine clusters of comorbidity. Latent classes were constructed based on the following cardiometabolic comorbidities using the "proc lca" procedure in SAS[118]: hypertension, hyperlipidemia/hypercholesterolemia, diabetes, peripheral vascular disease, systemic inflammatory

conditions (i.e., systemic lupus erythematosus, rheumatoid arthritis, etc.), hypothyroidism, cardiac arrhythmia, congestive heart failure, and coronary artery disease. Definitions and frequencies of each condition can be found in Appendix Table C.2.

Both three-class and four-class models were tested. Though the four-class model was statistically superior based on a bootstrapped parametric likelihood test, the three-class model was determined to be more clinically meaningful given its simpler utility. The three-class model consisted of: one class with moderate probability of hypertension ("HTN Only"; n = 37,032), one class with high probability of high cholesterol and hypertension and moderate probability of diabetes ("MetS", n = 36,889), and one class with high probability of hypertension, high cholesterol, cardiac arrhythmias, coronary artery disease (CAD), and congestive heart failure (CHF), and moderate probability of diabetes and peripheral vascular disease ("MetS+CVD"; n = 7,950). Following latent class construction, a 6-level categorical variable was constructed to represent the levels of latent class with or without obesity. Reference groups for subsequent analyses were "HTN Only", non-obese, or "HTN Only/Non-Obese", as appropriate.

Potential Mediators

The following variables were considered as possible mediators of the relationship between the latent class and obesity variables and the outcome of AKI: general anesthetic use (yes/no), blood product transfusion (yes/no), use of nephrotoxic medications (yes/no), total fluid volume administered (continuous, per 500mL), and minutes of hypotension defined as the number of minutes with a mean arterial pressure (MAP) <65mmHg (continuous)[14]. Due to the zero-inflated nature of the hypotension mediator, number of minutes >50th percentile and >75th percentile were considered as possible mediators. These intraoperative characteristics were selected to be considered as mediators as they represent potentially modifiable risk factors for AKI in this population.

Additional Covariates

The following variables were considered as covariates for the analysis: age at time of surgery (years), sex, self-reported race, preoperative estimated glomerular filtration rate (eGFR), self-reported smoking status (current smoker, former smoker, never smoker, unknown), year of case, surgical type

(knee vs. hip), American Society of Anesthesiologists (ASA) physical status, use of tranexamic acid (yes/no), and institution. Covariates were selected given known associations with postoperative development of AKI following surgery.

Statistical Methodology

Descriptive statistics are presented as frequencies with percentages for categorical variables and means with standard deviations or medians with interquartile ranges for continuous variables, as appropriate. Continuous data was assessed for normality using histograms, the Kolmogorov-Smirnov test, and Q-Q plots. Univariate comparisons between those with and without AKI were computed using chi-squared or Fisher's exact tests for categorical variables and either independent t-tests or Wilcoxon rank-sum tests for continuous variables, as appropriate. Standardized differences between those with and without AKI were computed. A p-value of 0.05 was considered statistically significant for all analyses. A complete case analysis was conducted. Analysis was conducted using SAS v. 9.4 (SAS Institute, Cary, NC) and RStudio version 1.4.

Mediation analysis is conducted under the following assumptions: confounding of the exposure-outcome relationship is controlled for, confounding of the mediator-outcome relationship is controlled for, confounding of the exposure-mediator relationship is controlled for, and there is no causal effect of the exposure on a confounder of the mediator-outcome relationship[128]. To the best of our knowledge these assumptions are held in the following analysis.

Prior to assessment of mediation effects, two sets of models were constructed to determine unadjusted associations between the mediators and AKI, and latent class/obesity group and the mediators of interest. To assess the relationship between mediators and AKI, a bivariate logistic regression model was constructed separately for each mediator, with the outcome of AKI, and the predictor variable the mediator of interest. A statistically significant univariate association, determined by $p < 0.05$, was evidence that there was an association between the mediator and the outcome. To assess the relationship between latent class/obesity group and the mediators, a bivariate logistic or linear regression model was constructed, as appropriate, with the outcome of the mediator and the predictor variable the latent

class/obesity group. A statistically significant univariate association, determined by $p < 0.05$ for at least one latent class/obesity group, was evidence that there was an association between the latent class/obesity group and the mediator of interest.

Mediation analyses were conducted separately for each mediator of interest that had a statistically significant univariate association with the outcome and with exposure (latent class, obesity status, or latent class/obesity interaction) and maintained that significance in fully adjusted models. Mediator-exposure interactions were assessed for each mediator-exposure combination. Covariates were held constant across all models. All potential mediators were included in all models. Mediation was conducted using the "mediation" package in R for causal mediation[129], which allows for a robust mediation analysis for a binary outcome variable and both binary and continuous potential mediators. A 100-sample non-parametric bootstrap was used to create confidence intervals. E-values were computed as a sensitivity analysis[130].

Given the non-binary exposure variable (latent class and obesity interaction), the following equation represents the average causal mediation effect, defined as the difference between the outcome predictions under each exposure status, computed using non-parametric inference between the group of interest and the reference exposure group ("HTN Only/Non-obese"):

$$\delta^{(j)}(t) = \frac{1}{nK}\sum_{i=1}^{n}\sum_{k=1}^{K}(Y_i^{(jk)}\left(t, M_i^{(jk)}(t_1)\right) - Y_i^{(jk)}\left(t, M_i^{(jk)}(t_0)\right))$$

Where t_1 is the exposure level of interest, t_0 is the exposure reference group, $M_i^{(jk)}(t)$ a set of simulated potential mediator values of length *k* for a given bootstrapped sample *j* of size *n* under each exposure status, and $Y_i^{(jk)}\left(t, M_i^{(jk)}(t)\right)$ the simulated set of potential outcome predictions for each exposure status and predicted mediators[131].

3.4. Results

Distribution of cardiometabolic comorbidities within each latent class can be found in Appendix Figure C.1. Of the 81,871 participants in the analytic sample (Appendix Figure C.2), a total of 45,214 (55.2%) were obese. Those in the "HTN Only" class had the lowest prevalence of obesity (47.5%), while 62.0% of the "MetS" class and 60.3% of the "MetS+CVD" class had obesity (Table 3.1). Within each latent class, those with obesity had 30-90% higher odds of AKI than those without obesity (Appendix Table C.3). There were significant differences in age, ASA status, and procedural characteristics across cardiometabolic latent classes and obesity groups (Tables 3.1-3.4). In general, those with more comorbidity were older with a higher ASA status, and had less time with a mean arterial pressure under 65mmHg.

Of the five mediators that were considered, three were statistically significantly associated with AKI in bivariate logistic regression models: general anesthesia use (unadjusted OR (UOR) 1.8, 95% CI: 1.6, 1.9; $p < 0.001$), use of PRBC (UOR 3.5, 95% CI: 2.8, 4.5; $p < 0.001$), and >12 minutes of hypotension (UOR 0.9, 95%CI: 0.8, 0.9; $p = 0.001$; Table 3.5). There was no statistically significant bivariate association with AKI for nephrotoxic medication use ($p = 0.114$) and total crystalloid volume ($p = 0.950$). Bivariate regression associations between the potential mediators and the variables of cardiometabolic latent class and obesity groups are presented in Table 3.6. For all potential mediators of interest except nephrotoxic medication use, at least level of exposure had a significantly lower odds of the mediator of interest when compared to the reference category.

Because nephrotoxic medication use and total crystalloid equivalents were not statistically significantly associated with AKI, they did not meet the definition of a mediator and were thus excluded from further analysis. In addition, PRBC use was also excluded as a possible mediator due to the small number of individuals receiving this intervention (n = 531).

Mediation Analysis: *General Anesthesia Use*

There was no statistically significant interaction between exposures of interest and the mediator of general anesthesia. Both obesity and cardiometabolic latent class were independently associated with

increased odds of general anesthesia use in the mediator model and AKI in the outcome model (Table 3.7). Similarly, in the model with cardiometabolic latent class and obesity interaction, all levels were significantly associated with AKI (Table 3.8). There were very small statistically significant but not clinically meaningful indirect effects of exposure level through general anesthesia use on AKI, with a range in risk difference of -0.04 per 100 cases (95%CI: -0.05, -0.02; "MetS"/Non-obese compared to "HTN Only"/Non-obese) to 0.14 per 100 cases (95%CI: 0.09, 0.19; "MetS+CVD"/Obese compared to "HTN Only"/Non-obese; Figure 3.1, Appendix Tables 3.4a-c). The size of the direct effect of exposure level compared to the reference ranged from a risk difference of 0.73 per 100 cases (95%CI: 0.31, 1.19; "MetS"/Non-obese compared to "HTN Only"/Non-obese) to 5.56 per 100 cases (95%CI: 4.92, 6.37; "MetS+CVD"/Obese compared to "HTN Only"/Non-obese).

A sensitivity analysis e-value of 6.12 (95%CI: 5.27, 7.20) was computed as the effect size needed of an unmeasured confounder to change the association between the "MetS+CVD"/Obese group compared to the reference and AKI. A sensitivity analyses testing the mediation effect sizes across all possible covariate combinations for the "MetS+CVD"/Obese group is shown in Appendix Figure C.3.

Mediation Analysis: *>12 Minutes of Intraoperative Hypotension*

There was a statistically significant interaction between the exposure of obesity and the mediator of >12 minutes of intraoperative hypotension, and between the exposure of cardiometabolic latent class/obesity group and the mediator. There was no statistically significant interaction between cardiometabolic latent class alone and intraoperative hypotension (Tables 3.9-3.11). Similar to the mediator of general anesthesia, there were very small statistically significant but not clinically meaningful indirect effects of exposure level through >12 minutes of intraoperative hypotension on AKI, with a range in risk difference of -0.03 per 100 cases (95%CI: -0.06, -0.01; "HTN Only"/Obese compared to "HTN Only"/Non-obese; Figure 3.2, Appendix Tables 3.5a-c) to -0.01 per 100 cases (95%CI: -0.03, -0.00; "MetS" compared to "HTN Only"). The size of the direct effect of exposure level compared to the reference ranged from a risk difference of 0.74 per 100 cases (95%CI: 0.32, 1.20; "MetS"/Non-obese

compared to “HTN Only”/Non-obese) to 5.46 per 100 cases (95%CI: 4.74, 6.18; “MetS+CVD”/Obese compared to “HTN Only”/Non-obese).

3.5. Discussion

In this multicenter cohort of elective total knee and hip arthroplasty patients, we found little evidence of a clinically significant mediating effect of general anesthesia use or minutes of hypotension on the relationship between preoperative cardiometabolic comorbidity and acute kidney injury. This suggests that while these factors are independent risk factors for acute kidney injury, controlling these factors intraoperatively may not meaningfully reduce the risk of AKI conferred by cardiometabolic comorbidity. Consideration of postoperative monitoring for those at high cardiometabolic risk for AKI may therefore be beneficial regardless of anesthetic protocol.

As a curative treatment for AKI does not exist, preventative management of perioperative risk factors largely remains the most effective practice in reducing the rate of AKI[20]. Common practices in high-risk patients include optimizing fluid management to avoid hypo- and hypervolemia, minimizing use of diuretics, reducing the need for unnecessary blood transfusions, and minimizing the time with hypotension[20]. We observed that in the mediator model for hypotension in our study, all levels of comorbidity were associated with lower odds of significant duration of hypotension than the reference group (“HTN Only”/Non-obese, “HTN Only”, or non-obese, respectively for each model). This may suggest that anesthetists are mindful of minimizing hypotension in those patients with more cardiometabolic comorbidity. We did not, however, see a clinically meaningful mediation effect of hypotension in our total joint arthroplasty population. Thus, while reducing time spent hypotensive does not confer additional risk for AKI based upon our data, it also may not mitigate the AKI risk inferred by cardiometabolic disease.

The use of general anesthesia, here assessed as a mediator, does not appear in recommended guidelines to reduce AKI risk despite the consistent association with AKI[20]. While not a modifiable risk factor in all surgical populations such as longer or more complex procedures, the use of neuraxial anesthetic techniques in total joint arthroplasty patients has been widely evaluated. Patients who receive

only neuraxial anesthesia have lower rates of postoperative outcomes including length of stay, cardiovascular complications, and AKI compared to those receiving general anesthesia[132,133]. However, neuraxial anesthetic techniques are contraindicated in some patients, including those with significant coagulopathy from medications to treat coronary artery and peripheral vascular disease or from medical conditions[134]. The results of our mediation analysis suggest that there may be no significant mechanism of action of cardiometabolic disease or obesity on AKI through general anesthetic use. Thus, the choice of one anesthetic technique over another likely has little effect on the pre-existing risk of postoperative AKI from cardiometabolic comorbidity.

Though we expected to see a clinically significant mediation effect of these modifiable risk factors on the association between preoperative cardiometabolic comorbidity and AKI, it is not surprising that a meaningful association was not present. Preoperative factors associated with AKI are generally thought to damage the kidney's vascular structure over time, making the organ less able to adequately respond to the additional stressors from a surgical procedure. Obesity may increase the risk of AKI through an increase in inflammatory cytokines and a higher blood volume providing constant stress on the organ prior to surgery[55,84,87]. Although many studies have found diabetes to be associated with AKI, the exact mechanism of action is unknown. It has been hypothesized that the increased risk of AKI is related to vascular damage from a hyperglycemic state, and in more severe cases of diabetes may also be related to atherosclerosis changes within the kidney which would reduce functionality[88]. Similar mechanistic consequences are likely in the presence of hypertension and other cardiometabolic diseases. Given the mechanical changes in the presence of these conditions, it is therefore unsurprising that intraoperative factors did not meaningfully mediate the risk of AKI in our population. Overall, our results suggest that while modifying intraoperative factors may reduce additional independent risk of AKI, doing so does not meaningfully mitigate risk conferred by cardiometabolic disease. Future work is needed to more fully elucidate the processes by which these diseases contribute to postoperative AKI.

This study has several strengths, most notably the multi-center nature of the cohort. This increases the generalizability of the findings, as they are less affected by institutional-level standard

intraoperative practices; however, the results may not be generalizable to other surgical procedures where these intraoperative factors may be influenced by procedural characteristics – for example, laparoscopic procedures of the torso increase intraabdominal pressure, which can in turn lead to hypotension[135]. Additionally, the large sample size of over 80,000 joint arthroplasty patients allowed for a robust cohort of those with the cardiometabolic conditions of interest and those with AKI for this mediation analyses. The multi-factorial definition of cardiometabolic comorbidity hopefully reduced misclassification bias due to the retrospective nature of the data. The study has a few limitations, most notably that the findings of this study may not be generalizable to a broader surgical cohort, particularly those where surgery type significantly increases the risk of AKI such as cardiovascular or intra-abdominal procedures. This is particularly of concern because the total joint arthroplasty population is often selected at the institutional level to be healthier with fewer comorbidities, as discussed in Chapter 2. Thus, the results of our analyses likely underestimate the true effects for both the direct and indirect effects. Additionally, the potential for unmeasured confounding is always a concern for mediation analyses; however, our computed e-value of 6.12 suggests that only a very strong unmeasured confounder could affect the results seen.

3.6. Conclusion

In this multicenter cohort of total knee and hip arthroplasty patients, we found little evidence of clinically significant mediation effect of general anesthesia use or intraoperative hypotension on the relationship between cardiometabolic comorbidity and postoperative acute kidney injury. Consideration of postoperative monitoring for those at high cardiometabolic risk for AKI should therefore be taken into account regardless of anesthetic protocol when considering where to perform these elective procedures.

Table 3.1. Population characteristics by cardiometabolic latent class group

	Hypertension Only (N = 37,032)	Metabolic Syndrome (N = 36,889)	Metabolic Syndrome and Cardiovascular Disease (N = 7,950)	Absolute Standardized Differences (HTN Only vs MetS)	Absolute Standardized Differences (HTN Only vs MetS+CVD)	Absolute Standardized Differences (MetS vs MetS+CVD)
Demographics						
Age				0.506	0.872	0.413
18-29	473 (1.3)	37 (0.1)	9 (0.1)			
30-39	967 (2.6)	122 (0.3)	11 (0.1)			
40-49	3,223 (8.7)	1,001 (2.7)	97 (1.2)			
50-59	9,671 (26.1)	6,097 (16.5)	699 (8.8)			
60-69	13,009 (35.1)	13,981 (37.9)	2,373 (29.9)			
70-79	7,520 (20.3)	12,068 (32.7)	3,182 (40.0)			
80+	2,169 (5.9)	3,583 (9.7)	1,579 (19.9)			
Female Sex	23,639 (63.8)	21,945 (59.5)	3,529 (44.4)	0.089	0.398	0.306
Race				0.043	0.138	0.127
Non-Hispanic White	27,902 (75.4)	27,637 (74.9)	6,349 (79.9)			
Non-Hispanic Black	4,799 (13.0)	5,237 (14.2)	983 (12.4)			
Hispanic	387 (1.1)	387 (1.1)	66 (0.8)			
Other	3,944 (10.7)	3,628 (9.8)	552 (6.9)			
ASA Class				0.477	1.382	0.844
1	1,362 (3.4)	161 (0.4)	2 (0.0)			
2	22,502 (60.8)	15,687 (42.5)	824 (10.4)			
3	12,874 (34.8)	20,485 (55.5)	6,358 (80.0)			
4	294 (0.8)	556 (1.5)	766 (9.6)			
Smoking Status				0.045	0.116	0.082
Current Smoker	3,429 (9.3)	3,305 (9.0)	810 (10.2)			
Former Smoker	714 (1.9)	954 (2.6)	294 (3.7)			
Never Smoker	4,449 (12.0)	4,423 (12.0)	867 (10.9)			
Unknown	28,440 (76.8)	28,207 (76.5)	5,979 (75.2)			
Obesity Combined	17,564 (47.4)	22,859 (62.0)	4,791 (60.3)	0.295	0.260	0.035
Cardiometabolic Comorbidities						
Hypertension	22,026 (59.5)	36,046 (97.7)	7,719 (97.1)	1.054	1.025	0.039
High Cholesterol	6,191 (16.7)	32,659 (88.5)	6,454 (81.2)	2.070	1.687	0.206
Peripheral Vascular Disorders	637 (1.7)	1,031 (2.8)	2,687 (33.8)	0.072	0.925	0.875
Diabetes	505 (1.4)	13,629 (37.0)	2,791 (35.1)	1.014	0.972	0.038
Systemic Inflammatory Disorders	3,341 (9.0)	1,596 (4.3)	656 (8.3)	0.189	0.027	0.162
Hypothyroidism	5,367 (14.5)	7,224 (19.6)	1,701 (21.4)	0.136	0.181	0.045
Cardiac Arrhythmias	4,570 (12.3)	5,512 (14.9)	5,678 (71.4)	0.076	1.495	1.388
Congestive Heart Failure	325 (0.9)	0 (0.0)	4,104 (51.6)	0.133	1.412	1.461
Coronary Artery Disease	135 (0.4)	5,041 (13.7)	5,418 (68.2)	0.539	2.041	1.331
Intraoperative Characteristics						
Procedure Type				0.200	0.113	0.086
Knee	19,257 (52.0)	22,823 (61.9)	4,582 (57.6)			

Hip	17,775 (48.0)	14,066 (38.1)	3,368 (42.4)			
Use of General Anesthesia	13,895 (37.5)	13,358 (36.2)	3,468 (43.6)	0.027	0.125	0.152
Packed Red Blood Cell Transfusion	242 (0.7)	179 (0.5)	110 (1.4)	0.022	0.073	0.094
Total Fluid Volume, Crystalloid Equivalents (per 500mL)	3.0 [2.0 to 4.0]	2.8 [2.0 to 4.0]	2.6 [1.8 to 4.0]	0.059	0.098	0.054
Minutes of MAP <65	4.0 [0.0 to 15.0]	3.0 [0.0 to 12.0]	2.0 [0.0 to 10.0]	0.098	0.211	0.112
Tranexamic acid use	25,384 (68.6)	24,747 (67.1)	4,330 (54.5)	0.031	0.293	0.261
Nephrotoxic Medication Use	32,898 (88.8)	32,728 (88.7)	7,112 (89.5)	0.004	0.020	0.024
Outcome						
Acute kidney injury	1,062 (2.9)	2,020 (5.6)	941 (11.8)	0.131	0.349	0.228

Data are presented as frequency (percentage) or median [25th percentile to 75th percentile], as appropriate. An absolute standardized difference >0.20 indicates the potential for significant heterogeneity between groups. Abbreviations: HTN = Hypertension; MetS = Metabolic Syndrome; CVD = Cardiovascular Disease; ASA = American Society of Anesthesiologists; MAP = Mean Arterial Pressure

Table 3.2. Population characteristics by obesity status

	Non-Obese (N = 36,657)	Obese (N = 45,214)	Absolute Standardized Differences
Demographics			
Age			0.373
18-29	347 (1.0)	172 (0.4)	
30-39	617 (1.7)	483 (1.1)	
40-49	1,644 (4.5)	2,677 (5.9)	
50-59	6,049 (16.5)	10,418 (23.0)	
60-69	11,636 (31.7)	17,727 (39.2)	
70-79	11,404 (31.1)	11,366 (25.1)	
80+	4,960 (13.5)	2,371 (5.2)	
Female Sex	21,393 (58.4)	27,720 (61.3)	0.060
Race			0.241
Non-Hispanic White	28,625 (78.1)	33,263 (73.6)	
Non-Hispanic Black	3,413 (9.3)	7,606 (16.8)	
Hispanic	323 (0.9)	517 (1.1)	
Other	4,296 (11.7)	3,828 (8.5)	
ASA Class			0.403
1	1,233 (3.4)	292 (0.7)	
2	20,640 (56.3)	18,373 (40.6)	
3	14,146 (38.6)	25,571 (56.6)	
4	638 (1.7)	978 (2.2)	
Smoking Status			0.042
Current Smoker	3,284 (9.0)	4,260 (9.4)	
Former Smoker	871 (2.4)	1,091 (2.4)	
Never Smoker	4,124 (11.3)	5,615 (12.4)	
Unknown	28,378 (77.4)	34,248 (75.8)	
Cardiometabolic Comorbidities			
Hypertension	26,999 (73.7)	38,792 (85.8)	0.306
High Cholesterol	18,757 (51.2)	26,547 (58.7)	0.152
Peripheral Vascular Disorders	1,934 (5.3)	2,421 (5.4)	0.004
Diabetes	4,570 (12.5)	12,355 (27.3)	0.379
Systemic Inflammatory Disorders	2,672 (7.3)	2,921 (6.5)	0.033
Hypothyroidism	6,105 (16.7)	8,187 (18.1)	0.038
Cardiac Arrhythmias	6,945 (19.0)	8,815 (19.5)	0.014
Congestive Heart Failure	1,628 (4.4)	2,801 (6.2)	0.078
Coronary Artery Disease	4,396 (12.0)	6,198 (13.7)	0.051
Cardiometabolic Latent Class			0.051
Hypertension Only	19,468 (53.1)	22,859 (50.6)	
Metabolic Syndrome	14,030 (38.3)	17,564 (38.9)	
Metabolic Syndrome + Cardiovascular Disease	3,159 (8.6)	4,791 (10.6)	
Intraoperative Characteristics			
Procedure Type			0.342

Knee	17,505 (47.8)	29,157 (64.5)	
Hip	19,152 (52.3)	16,057 (35.5)	
Use of General Anesthesia	13,305 (36.3)	17,416 (38.5)	0.046
Packed Red Blood Cell Transfusion	320 (0.9)	211 (0.5)	0.050
Total Fluid Volume, Crystalloid Equivalents (per 500mL)	2.8 [2.0 to 4.0]	2.8 [2.0 to 4.0]	0.022
Minutes of MAP <65	4.0 [0.0 to 14.0]	3.0 [0.0 to 12.0]	0.082
Tranexamic acid use	24,503 (66.8)	29,958 (66.3)	0.012
Nephrotoxic Medication Use	32,778 (89.4)	39,960 (88.4)	0.033
Outcome			
Acute kidney injury	1,213 (3.3)	2,810 (6.2)	0.137

Data are presented as frequency (percentage) or median [25th percentile to 75th percentile], as appropriate. An absolute standardized difference >0.20 indicates the potential for significant heterogeneity between groups. Abbreviations: ASA = American Society of Anesthesiologists; MAP = Mean Arterial Pressure

Table 3.3. Population characteristics by latent class and obesity interaction

	Hypertension Only		Metabolic Syndrome		Metabolic Syndrome and Cardiovascular Disease	
	Non-Obese N = 19,468	**Obese** N = 17,564	**Non-Obese** N = 14,030	**Obese** N = 22,859	**Non-Obese** N = 3,159	**Obese** N = 4,791
Demographics						
Age						
18-29	320 (1.6)	153 (0.9)	20 (0.1)	17 (0.1)	7 (0.2)	2 (0.0)
30-39	560 (2.9)	407 (2.3)	50 (0.4)	72 (0.3)	7 (0.2)	4 (0.1)
40-49	1,403 (7.2)	1,820 (10.4)	227 (1.6)	774 (3.4)	14 (0.4)	83 (1.7)
50-59	4,354 (22.4)	5,317 (30.3)	1,522 (10.9)	4,575 (20.0)	173 (5.5)	526 (11.0)
60-69	6,515 (33.5)	6,494 (37.0)	4,464 (31.8)	9,517 (41.6)	657 (20.8)	1,716 (35.8)
70-79	4,613 (23.7)	2,907 (16.6)	5,470 (39.0)	6,598 (28.9)	1,321 (41.8)	1,861 (38.8)
80+	1,703 (8.8)	466 (2.7)	2,277 (16.2)	1,306 (5.7)	980 (31.0)	599 (12.5)
Female Sex	12,065 (62.0)	11,574 (65.9)	7,981 (56.9)	13,964 (61.1)	1,347 (42.6)	2,182 (45.5)
Race						
Non-Hispanic White	15,135 (77.7)	2,630 (83.3)	10,860 (77.4)	16,777 (73.4)	2,630 (83.3)	3,719 (77.6)
Non-Hispanic Black	1,783 (9.2)	265 (8.4)	1,365 (9.7)	3,872 (16.9)	265 (8.4)	718 (15.0)
Hispanic	176 (0.9)	22 (0.7)	125 (0.9)	262 (1.2)	22 (0.7)	44 (0.9)
Other	2,374 (12.2)	242 (7.7)	1,680 (12.0)	1,948 (8.5)	242 (7.7)	310 (6.5)
ASA Class						
1	1,123 (5.8)	239 (1.4)	109 (0.8)	52 (0.2)	1 (0.0)	1 (0.0)
2	12,993 (66.7)	9,509 (54.1)	7,276 (51.9)	8,411 (36.8)	371 (11.7)	453 (9.5)
3	5,205 (26.7)	7,669 (43.7)	6,455 (46.0)	14,030 (61.4)	2,486 (78.7)	3,872 (80.8)
4	147 (0.8)	147 (0.8)	190 (1.4)	366 (1.6)	301 (9.5)	465 (9.7)
Smoking Status						
Current Smoker	1,778 (9.1)	1,651 (9.4)	1,168 (8.3)	2,137 (9.4)	338 (10.7)	472 (9.9)
Former Smoker	391 (2.0)	323 (1.8)	372 (2.7)	582 (2.6)	108 (3.4)	186 (3.9)
Never Smoker	2,174 (11.2)	2,275 (13.0)	1,610 (11.5)	2,813 (12.3)	340 (10.8)	527 (11.0)
Unknown	15,125 (77.7)	13,315 (75.8)	10,880 (77.6)	17,327 (75.8)	2,373 (75.1)	3,606 (75.3)
Cardiometabolic Comorbidities						
Hypertension	10,296 (52.9)	11,730 (66.8)	13,671 (97.4)	22,375 (97.9)	3,032 (96.0)	4,687 (97.8)
High Cholesterol	3,552 (18.3)	2,639 (15.0)	12,703 (90.5)	19,956 (87.3)	2,502 (79.2)	3,952 (82.5)
Peripheral Vascular Disorders	320 (1.6)	317 (1.8)	442 (3.2)	589 (2.6)	1,172 (37.1)	1,515 (31.6)
Diabetes	206 (1.1)	299 (1.7)	3,650 (26.0)	9,979 (43.7)	714 (22.6)	2,077 (43.4)
Systemic Inflammatory Disorders	1,794 (9.2)	1,547 (8.8)	620 (4.4)	976 (4.3)	258 (8.2)	398 (8.3)
Hypothyroidism	2,661 (13.7)	2,706 (15.4)	2,730 (19.5)	4,494 (19.7)	714 (22.6)	987 (20.6)
Cardiac Arrhythmias	2,467 (12.7)	2,103 (12.0)	2,150 (15.3)	3,362 (14.7)	2,328 (73.7)	3,350 (69.9)
Congestive Heart Failure	149 (0.8)	176 (0.8)	0 (0.0)	0 (0.0)	1,479 (46.8)	2,625 (54.8)
Coronary Artery Disease	87 (0.5)	48 (0.3)	2,055 (14.7)	2,986 (13.1)	2,254 (71.4)	3,164 (66.0)
Intraoperative Characteristics						
Procedure Type						
Knee	8,549 (43.9)	10,708 (61.0)	7,423 (52.9)	15,400 (67.4)	1,533 (48.5)	3,049 (63.6)
Hip	10,919 (56.1)	6,856 (39.0)	6,607 (47.1)	7,459 (32.6)	1,626 (51.5)	1,742 (36.4)
Use of General Anesthesia	7,275 (37.4)	6,620 (37.7)	4,713 (33.6)	8.645 (37.8)	1,317 (41.7)	2,151 (44.9)

Packed Red Blood Cell Transfusion	171 (0.9)	71 (0.4)	93 (0.7)	86 (0.4)	56 (1.8)	54 (1.1)
Total Fluid Volume, Crystalloid Equivalents (per 500mL)	2.9 [2.0 to 4.0]	3.0 [2.0 to 4.0]	2.7 [2.0 to 4.0]	2.8 [2.0 to 4.0]	2.5 [1.6 to 3.8]	2.6 [1.8 to 4.0]
Minutes of MAP <65	5.0 [0.0 to 16.0]	3.0 [0.0 to 13.0]	3.0 [0.0 to 13.0]	3.0 [0.0 to 12.0]	3.0 [0.0 to 10.0]	2.0 [0.0 to 10.0]
Tranexamic acid use	13,503 (69.4)	11,881 (67.6)	9,314 (66.4)	15,433 (67.5)	1,686 (53.4)	2,644 (55.2)
Nephrotoxic Medication Use	17,422 (89.5)	15,476 (88.1)	12,518 (89.2)	20,210 (88.4)	2,838 (89.8)	4,274 (89.2)
Outcome						
Acute kidney injury	401 (2.1)	661 (3.8)	507 (3.6)	1,513 (6.6)	305 (9.7)	636 (13.3)

Data are presented as frequency (percentage) or median [25th percentile to 75th percentile], as appropriate. An absolute standardized difference >0.20 indicates the potential for significant heterogeneity between groups. Abbreviations: HTN = Hypertension; MetS = Metabolic Syndrome; CVD = Cardiovascular Disease; ASA = American Society of Anesthesiologists; MAP = Mean Arterial Pressure

Table 3.4. Absolute standardized differences compared to the hypertension only/non-obese group.

	Hypertension Only	Metabolic Syndrome		Metabolic Syndrome and Cardiovascular Disease	
	Obese N = 17,564	Non-Obese N = 14,030	Obese N = 22,859	Non-Obese N = 3,159	Obese N = 4,791
Demographics					
Age	0.374	0.605	0.382	1.001	0.586
Female Sex	0.082	0.104	0.018	0.395	0.334
Race	0.253	0.020	0.252	0.161	0.254
ASA Class	0.411	0.481	0.802	1.588	1.695
Smoking Status	0.058	0.051	0.054	0.104	0.115
Cardiometabolic Comorbidities					
Hypertension	0.286	1.204	1.225	1.136	1.222
High Cholesterol	0.087	2.110	1.915	1.539	1.677
Peripheral Vascular Disorders	0.012	0.099	0.065	1.004	0.879
Diabetes	0.055	0.784	1.190	0.708	1.182
Systemic Inflammatory Disorders	0.014	0.191	0.198	0.037	0.032
Hypothyroidism	0.049	0.156	0.161	0.233	0.182
Cardiac Arrhythmias	0.021	0.077	0.059	1.564	1.429
Congestive Heart Failure	0.025	0.124	0.124	1.286	1.512
Coronary Artery Disease	0.029	0.558	0.519	2.194	1.940
Intraoperative Characteristics					
Procedure Type	0.347	0.181	0.486	0.093	0.404
Use of General Anesthesia	0.007	0.079	0.009	0.089	0.153
Packed Red Blood Cell Transfusion	0.059	0.025	0.064	0.078	0.025
Total Fluid Volume, Crystalloid Equivalents (per 500mL)	0.023	0.077	0.039	0.123	0.084
Minutes of MAP <65	0.118	0.141	0.160	0.253	0.274
Tranexamic acid use	0.037	0.064	0.040	0.333	0.296
Nephrotoxic Medication Use	0.044	0.009	0.034	0.011	0.009
Outcome					
Acute kidney injury	0.102	0.094	0.225	0.328	0.431

An absolute standardized difference >0.2 indicates the possibility of significant heterogeneity between groups. Abbreviations: HTN = Hypertension; MetS = Metabolic Syndrome; CVD = Cardiovascular Disease; ASA = American Society of Anesthesiologists; MAP = Mean Arterial Pressure

Table 3.5. Bivariate model results for the outcome of AKI with mediator as predictor of interest

	Unadjusted Odds Ratio	95% Confidence Interval	P-Value
General anesthesia use	1.76	1.65, 1.87	<0.001
Packed red blood cell use	3.53	2.78, 4.49	<0.001
Nephrotoxic medication use	1.09	0.98, 1.21	0.114
Minutes of hypotension			
Total minutes MAP <65mmHg	0.996	0.993, 0.999	0.004
>3 minutes of hypotension (50th centile)	0.98	0.92, 1.04	0.483
>12 minutes of hypotension (75th centile)	0.88	0.82, 0.95	0.001
Total crystalloid equivalent fluid volume (per 500mL)	1.00	0.99, 1.01	0.950

Table 3.6. Bivariate model results for the outcome of individual mediators with latent class group as predictor of interest

		General Anesthesia	**Packed Red Blood Cell Use**	**Nephrotoxic Medication Use**	**>12 Minutes of Hypotension MAP <65mmHg**	**Total crystalloid equivalent fluid volume (per 500mL)**
Cardiometabolic Latent Class						
Hypertension Only		Reference	Reference	Reference	Reference	Reference
Metabolic Syndrome		0.95 (0.92, 0.97)	0.74 (0.61, 0.90)	0.99 (0.94, 1.04)	0.82 (0.79, 0.85)	-0.15 (-0.19, -0.12)
Metabolic Syndrome + Cardiovascular Disease		1.29 (1.23, 1.35)	2.13 (1.70, 2.68)	1.07 (0.99, 1.15)	0.65 (0.61, 0.68)	-0.26 (-0.32, -0.20)
Obesity						
Non-Obese		Reference	Reference	Reference	Reference	Reference
Obese		1.10 (1.07, 1.13)	0.53 (0.45, 0.63)	0.90 (0.86, 0.94)	0.85 (0.82, 0.88)	0.05 (0.02, 0.09)
Cardiometabolic Latent Class and Obesity Interaction						
Hypertension Only	Non-Obese	Reference	Reference	Reference	Reference	Reference
	Obese	1.01 (0.97, 1.06)	0.46 (0.35, 0.60)	0.87 (0.82, 0.93)	0.79 (0.76, 0.83)	0.07 (0.02, 0.12)
Metabolic Syndrome	Non-Obese	0.85 (0.81, 0.89)	0.75 (0.58, 0.97)	0.97 (0.91, 1.04)	0.75 (0.72, 0.79)	-0.17 (-0.23, -0.11)
	Obese	1.02 (0.98, 1.06)	0.43 (0.33, 0.55)	0.90 (0.84, 0.95)	0.73 (0.70, 0.76)	-0.09 (-0.13, -0.04)
Metabolic Syndrome + Cardiovascular Disease	Non-Obese	1.20 (1.11, 1.29)	2.04 (1.50, 2.76)	1.04 (0.92, 1.18)	0.60 (0.55, 0.66)	-0.28 (-0.38, -0.19)
	Obese	1.37 (1.28, 1.46)	1.29 (0.95, 1.75)	0.97 (0.88, 1.08)	0.57 (0.52, 0.61)	-0.19 (-0.27, -0.11)

Data are presented as unadjusted odds ratio (95% confidence interval) for general anesthesia, pRBC use, >12 minutes hypotension, and nephrotoxic medication use; data are presented as unadjusted beta coefficients (95% confidence interval) for total crystalloid equivalent.

Table 3.7. Model results for outcome and mediation full models for the exposure of cardiometabolic latent class or obesity, and the mediator of general anesthesia use

	General Anesthesia Model Set		
	Parameter Estimate (Standard Error)	Odds Ratio (95% CI)	P-Value
Mediator and Exposure Variable in Outcome Model			
General anesthesia use	0.392 (0.037)	1.48 (1.38, 1.59)	<0.001
Obesity	0.538 (0.039)	1.71 (1.59, 1.85)	<0.001
Cardiometabolic Latent Class			
Hypertension Only	Reference	Reference	
Metabolic Syndrome	0.314 (0.041)	1.37 (1.26, 1.48)	<0.001
Metabolic Syndrome + Cardiovascular Disease	0.718 (0.054)	2.05 (1.84, 2.28)	<0.001
Exposure Variable in Mediator Model			
Obesity	0.183 (0.018)	1.20 (1.16, 1.24)	<0.001
Cardiometabolic Latent Class			
Hypertension Only	Reference	Reference	
Metabolic Syndrome	-0.045 (0.018)	0.96 (0.92, 0.99)	0.013
Metabolic Syndrome + Cardiovascular Disease	0.068 (0.031)	1.07 (1.01, 1.14)	0.018

Outcome and mediator models were additionally adjusted for age, estimated glomerular filtration rate, sex, race, obesity status, procedure type, ASA classification, smoking status, packed red blood cell transfusion, crystalloid equivalents given, nephrotoxic medication use, tranexamic acid use, year, and institution. The other mediator of interest (general anesthesia for the hypotension model, hypotension for the general anesthesia model) was not included in the modeling set.

Table 3.8. Model results for outcome and mediation full models for the exposure of cardiometabolic latent class and obesity group, and the mediator of general anesthesia use

	General Anesthesia Model Set		
	Parameter Estimate (Standard Error)	Odds Ratio (95% CI)	P-Value
Mediator and Exposure Variable in Outcome Model			
General anesthesia use	0.391 (0.037)	1.48 (1.38, 1.59)	<0.001
Latent Class/Obesity Interaction			
HTN Only/Non-obese	Reference	Reference	
HTN Only/Obese	0.536 (0.067)	1.71 (1.50, 1.95)	<0.001
MetS/Non-Obese	0.263 (0.070)	1.30 (1.13, 1.49)	<0.001
MetS/Obese	0.869 (0.061)	2.38 (2.12, 2.69)	<0.001
MetS + CVD/Non-obese	0.811 (0.086)	2.25 (1.90, 2.66)	<0.001
MetS + CVD/Obese	1.211 (0.073)	3.36 (2.91, 3.87)	<0.001
Exposure Variable in Mediator Model			
Latent Class/Obesity Interaction			
HTN Only/Non-obese	Reference	Reference	
HTN Only/Obese	0.074 (0.025)	1.08 (1.03, 1.13)	0.003
MetS/Non-Obese	-0.155 (0.027)	0.86 (0.81, 0.90)	<0.001
MetS/Obese	0.117 (0.024)	1.12 (1.07, 1.18)	<0.001
MetS + CVD/Non-obese	-0.060 (0.046)	0.94 (0.86, 1.03)	0.188
MetS + CVD/Obese	0.243 (0.039)	1.27 (1.18, 1.38)	<0.001

Outcome and mediator models were additionally adjusted for age, estimated glomerular filtration rate, sex, race, procedure type, ASA classification, smoking status, >12 minutes of hypotension, packed red blood cell transfusion, crystalloid equivalents given, nephrotoxic medication use, tranexamic acid use, year, and institution.

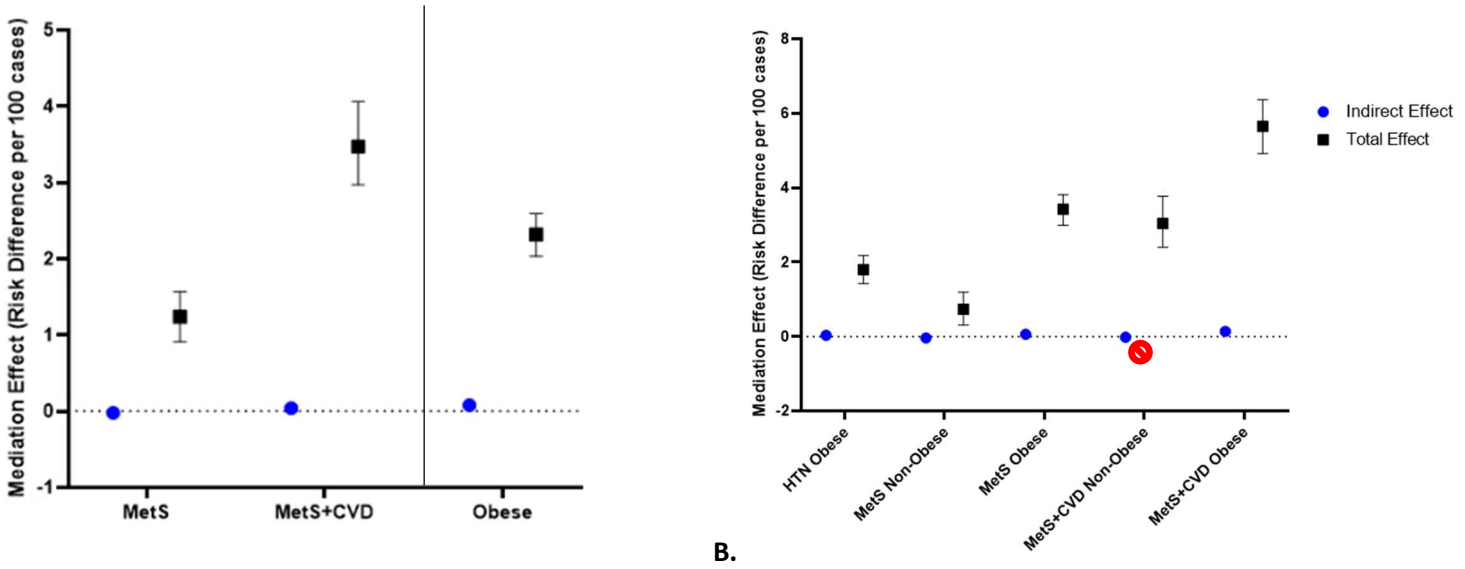


Figure 3.1. Total and indirect mediation effects for the three exposure-mediator combinations for the mediator of general anesthesia use. Panel A shows the results for the mediation model of cardiometabolic latent class (reference: "Hypertension Only") and the mediation model of obesity (reference: non-obese). Panel B shows the results for the mediation model of cardiometabolic latent class and obesity interaction (reference: "Hypertension Only"/non-obese). All effects were statistically significant with the exception of the indirect effect of the "MetS + CVD/Non-obese" group. Abbreviations: HTN = Hypertension; MetS = Metabolic Syndrome; CVD = Cardiovascular Disease.

Table 3.9. Model results for outcome and mediation full models for the exposure of cardiometabolic latent class and the mediator of >12 minutes of intraoperative hypotension

	>12 Minutes of Hypotension Model Set		
	Parameter Estimate (Standard Error)	Odds Ratio (95% CI)	P-Value
Mediator and Exposure Variable in Outcome Model			
>12 minutes of hypotension	0.112 (0.041)	1.12 (1.03, 1.21)	0.006
Cardiometabolic Latent Class			
Hypertension Only	Reference	Reference	
Metabolic Syndrome	0.314 (0.041)	1.37 (1.26, 1.48)	<0.001
Metabolic Syndrome + Cardiovascular Disease	0.718 (0.054)	2.05 (1.84, 2.28)	<0.001
Exposure Variable in Mediator Model			
Cardiometabolic Latent Class			
Hypertension Only	Reference	Reference	
Metabolic Syndrome	-0.088 (0.019)	0.92 (0.88, 0.95)	<0.001
Metabolic Syndrome + Cardiovascular Disease	-0.131 (0.035)	0.88 (0.82, 0.94)	<0.001

Outcome and mediator models were additionally adjusted for age, estimated glomerular filtration rate, sex, race, procedure type, ASA classification, smoking status, general anesthesia use, packed red blood cell transfusion, crystalloid equivalents given, nephrotoxic medication use, tranexamic acid use, year, and institution. There was no statistically significant interaction between exposure and mediator.

Table 3.10. Model results for outcome and mediation full models for the exposure of obesity and the mediator of >12 minutes of intraoperative hypotension

	>12 Minutes of Hypotension Model Set		
	Parameter Estimate (Standard Error)	Odds Ratio (95% CI)	P-Value
Mediator and Exposure Variable in Outcome Model			
>12 minutes of hypotension	-0.032 (0.072)	0.97 (0.84, 1.12)	0.657
Obesity	0.488 (0.044)	1.63 (1.50, 1.77)	<0.001
Hypo*obesity	0.209 (0.085)	1.23 (1.04, 1.46)	0.014
Exposure Variable in Mediator Model			
Obesity	-0.055 (0.018)	0.95 (0.91, 0.98)	0.003

Outcome and mediator models were additionally adjusted for age, estimated glomerular filtration rate, sex, race, procedure type, ASA classification, smoking status, general anesthesia use, packed red blood cell transfusion, crystalloid equivalents given, nephrotoxic medication use, tranexamic acid use, year, and institution. There was a statistically significant interaction between exposure and mediator, which is reflected in the model construction.

Table 3.11. Model results for outcome and mediation full models for the exposure of cardiometabolic latent class and obesity interaction, and the mediator of >12 minutes of intraoperative hypotension

	>12 Minutes of Hypotension Model Set		
	Parameter Estimate (Standard Error)	Odds Ratio (95% CI)	P-Value
Mediator and Exposure Variable in Outcome Model			
>12 minutes of hypotension	-0.256 (0.122)	0.77 (0.61, 0.98)	0.036
Latent Class/Obesity Interaction			
HTN Only/Non-obese	Reference	Reference	
HTN Only/Obese	0.401 (0.076)	1.49 (1.29, 1.73)	<0.001
MetS/Non-Obese	0.162 (0.080)	1.18 (1.01, 1.38)	0.042
MetS/Obese	0.754 (0.069)	2.13 (1.86, 2.43)	<0.001
MetS + CVD/Non-obese	0.733 (0.095)	2.08 (1.73, 2.51)	<0.001
MetS + CVD/Obese	1.136 (0.081)	3.11 (2.66, 3.65)	<0.001
Hypo*LCA/Obese Class			
HTN Only/Non-obese	Reference	Reference	
HTN Only/Obese	0.512 (0.151)	1.67 (1.24, 2.24)	0.001
MetS/Non-Obese	0.391 (0.161)	1.48 (1.08, 2.03)	0.015
MetS/Obese	0.444 (0.137)	1.56 (1.19, 2.04)	0.001
MetS + CVD/Non-obese	0.286 (0.200)	1.33 (0.90, 1.97)	0.151
MetS + CVD/Obese	0.265 (0.166)	1.30 (0.94, 1.81)	0.110
Exposure Variable in Mediator Model			
Latent Class/Obesity Interaction			
HTN Only/Non-obese	Reference	Reference	
HTN Only/Obese	-0.151 (0.025)	0.86 (0.82, 0.90)	<0.001
MetS/Non-Obese	-0.197 (0.027)	0.88 (0.78, 0.87)	<0.001
MetS/Obese	-0.147 (0.025)	0.82 (0.82, 0.91)	<0.001
MetS + CVD/Non-obese	-0.191 (0.051)	0.86 (0.75, 0.91)	<0.001
MetS + CVD/Obese	-0.221 (0.044)	0.83 (0.74, 0.87)	<0.001

Outcome and mediator models were additionally adjusted for age, estimated glomerular filtration rate, sex, race, procedure type, ASA classification, smoking status, general anesthesia use, packed red blood cell transfusion, crystalloid equivalents given, nephrotoxic medication use, tranexamic acid use, year, and institution. There was a statistically significant interaction between exposure and mediator, which is reflected in the model construction.

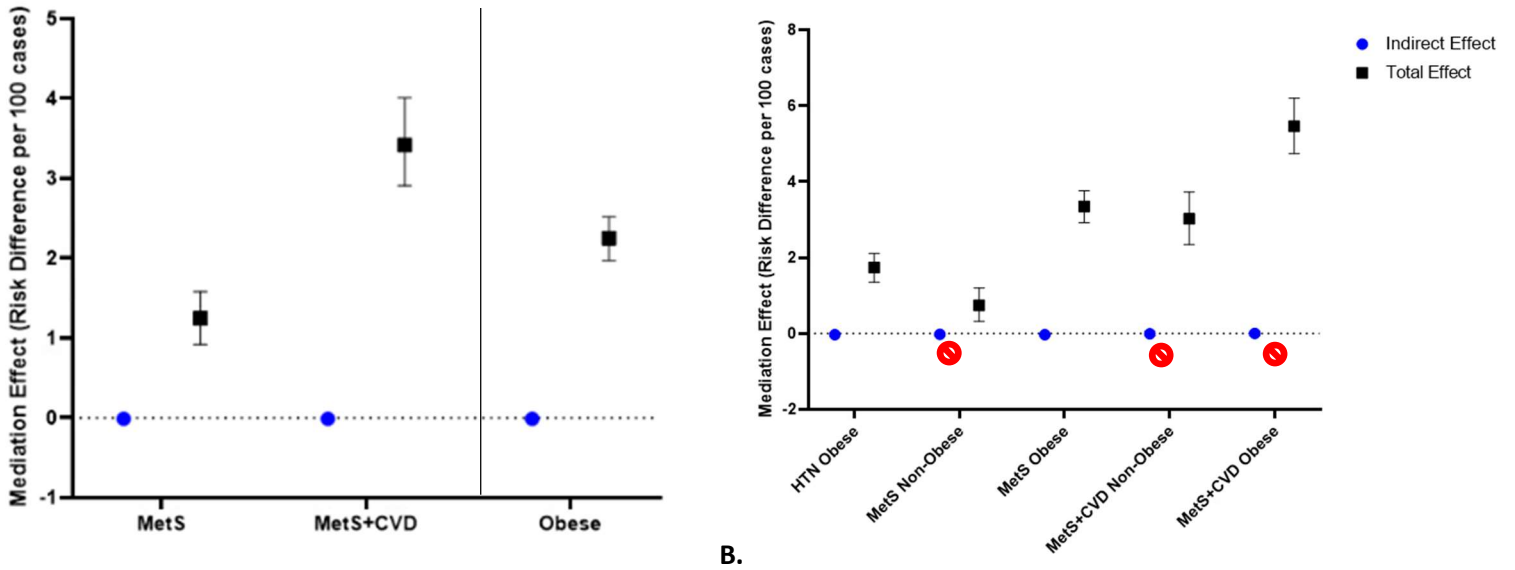


Figure 3.2. Total and indirect mediation effects for the three exposure-mediator combinations for the mediator of >12 minutes of intraoperative hypotension. There were statistically significant interactions between obesity/mediator and cardiometabolic latent class/obesity group and mediator; both are reflected in the model construction. Panel A shows the results for the mediation model of cardiometabolic latent class (reference: "Hypertension Only") and the mediation model of obesity (reference: non-obese). Panel B shows the results for the mediation model of cardiometabolic latent class and obesity interaction (reference: "Hypertension Only"/non-obese). All effects were statistically significant for the cardiometabolic class and obesity models. However, the indirect effects of >12 minutes of intraoperative hypotension were not statistically significant for the "MetS"/Non-obese, "MetS+CVD"/Non-obese, and "MetS+CVD"/Obese groups compared to the reference of "HTN Only"/Non-obese. Abbreviations: HTN = Hypertension; MetS = Metabolic Syndrome; CVD = Cardiovascular Disease.

Appendix C

Supplemental Material

Appendix Table C.1. Multicenter Perioperative Outcomes Group perioperative research standards

1. Has Valid Anesthesia Start time
2. Has Valid Anesthesia End time
3. Has a Valid Institution ID
4. Case Duration >15 minutes if Anesthesia Technique General = true
5. Case Duration >5 minutes if Anesthesia Technique General = false
6. Has an actual or predicted anesthesia CPT code
7. Has Age data
8. Has Sex data
9. Has valid ASA Class
10. Has Baseline Blood Pressure Mean
11. Has at least one intraoperative med administered
12. Has at least one ICD 9/10 discharge diagnoses
13. Has at least one creatinine or hematocrit within 365 days before/after surgery

Appendix Table C.2. Overall cardiometabolic comorbidity frequencies by definition type (N = 81,871)

	ICD Code Yes, n (%)	Physiologic/ Laboratory Yes, n (%)	History and Physical Yes, n (%)	Overall Yes, n (%)	ICD 9/10 Definition	Laboratory or Physiologic Definition
Hypertension	53,430 (65.3)	39,886 (48.7)	33,715 (41.2)	65,791 (80.4)	40[2-5], 40[2-5].%, I1[1,2,3,5].%, 401.%, 401, I10, I10.%	Baseline SBP ≥ 140mmHg or baseline DBP ≥ 90mmHg or baseline MAP >107mmHg
High Cholesterol	39,507 (48.3)	7,087 (8.7)	7,770 (9.5)	45,304 (55.3)	272.[0-4], E78.0, E78.[0-4]%, E78.5	Cholesterol ≥ 200mg/dL, or triglyceride ≥ 150mg/dL, or HDL cholesterol ≤ 40mg/dL for men and ≤ 50mg/dL for women, or LDL cholesterol ≥ 100mg/dL
Peripheral Vascular Disorders	4,273 (5.2)		151 (0.2)	4,355 (5.3)	093.0%, 437.3%, 443.[1–9]%, 447.1%, V43.4%, 44[0,1], 44[0,1].%, 557.[1,9]%, I77.1%, Z95.[8,9]%, I73.[1,8,9]%, I79.[0,2]%,K55.[1,8,9]%, I7[0,1].%	N/A
Diabetes	15,637 (19.1)	6,283 (7.7)	5,906 (7.2)	16,925 (20.7)	250.[4-9]%, E1[0-4].[2–8]%, 250.[0-3]%, E1[0-4].[0,1,9]%	HbA1c level ≥ 6.5%
Systemic Inflammatory Disorders	5,570 (6.8)		143 (0.2)	5,593 (6.8)	446, 446.%, 714, 714.%, 719.3%, 701.0%, 72[0,5], 72[0,5].%, 710.[0–4,8,9]%, 711.2%, 728.5%, 728.89, 729.30, M30.%, M31.[0–3]%, M0[5,6,8].%, M12.[0,3]%, L94.[0,1,3]%, M45.%, M46.[1,8,9]%, M3[2-5].%	N/A
Hypothyroidism	13,932 (17.0)	768 (0.9)	911 (1.1)	14,292 (17.5)	24[3,4], 24[3,4].%, 240.9%, 246.[1,8]%, E0[0-3], E0[0-3].%, E89.0%	Thyroid stimulating hormone laboratory level > 4.0 mU/L
Cardiac Arrhythmias	14,421 (17.6)		4,406 (5.4)	15,760 (19.3)	996.0[1,4], 426.[0,7,9]%, 426.1[0,2,3], 427.[0-4,6-9]%, 785.0%, V45.0%, V53.3%, T82.1%, I44[1-3].%, I45.[69]%, I4[7-9], I4[7-9].%, R00.[0,1,8]%, Z45.0%, Z95.0%	N/A
Congestive Heart Failure	4,014 (4.9)		1,421 (1.7)	4,429 (5.4)	425.[4–9]%, 428, 428.%, 404.[0,1,9]3, 40[2,4].[0,1,9]1, 398.91, I43, I43.%, I42.[0,5–9]%, I25.5%, 150, 150.%, I11.0%, I13.[0,2]%, I09.9%, P29.0%	N/A
Coronary Artery Disease	9,861 (12.0)		5,079 (6.2)	10,594 (12.9)	412, 414.2, 414.8, 414.9, V45.81, V45.82, I25.10, I25.110, I25.111,	N/A

				I25.118, I25.119, I25.2, I25.5, I25.6. I25.700, I25.701, I25.708, I25.709, I25.710, I25.711, I25.718, I25.719, I25.720, I25.721, I25.728, I25.729, I25.730, I25.731, I25.738, I25.739, I25.750, I25.751, I25.758, I25.759, I25.760, I25.761, I25.768, I25.769, I25.790, I25.791, I25.798, I25.799, I25.810, I25.811, I25.812, I25.82, I25.83, I25.84, I25.89, I25.9, Z95.1, Z95.5, Z98.61	
Obesity	28,736 (35.1)	41,634 (50.9)	45,214 (55.2)	278.0%, E66.%	Body mass index ≥ 30 kg/m^2

Note: Systemic inflammatory disorders includes conditions such as systemic lupus erythematosus and rheumatoid arthritis.

Appendix Table C.3. Unadjusted odds of AKI for those with obesity compared to those without, within each latent class

	Analytic Cohort (N = 81,871)
MetS	1.89 (1.71, 2.10)
Hypertension Only	1.86 (1.64, 2.11)
MetS and CVD	1.43 (1.24, 1.66)

Unadjusted odds ratios were computed using a bivariate logistic regression for the outcome of interest of AKI status. Abbreviations: MetS – metabolic syndrome, CVD – cardiovascular disease, CAD – coronary artery disease

Appendix Table C.4a. Estimated direct effect of cardiometabolic latent class with/without obesity and indirect effects of general anesthesia as a mediator on the outcome of acute kidney injury

			Risk Difference (95% CI)	Risk Difference per 100 cases (95% CI)	P-Value
Hypertension Only	Obese	Total	0.01804 (0.01417, 0.02171)	1.80 (1.42, 2.17)	<0.001
		Direct	0.01786 (0.01398, 0.02158)	1.79 (1.40, 2.16)	<0.001
		Total Indirect	0.00029 (0.00007, 0.00041)	0.03 (0.01, 0.04)	0.01
		Proportion Mediated	0.01598 (0.00327, 0.02477)	1.60 (0.33, 2.48)	0.01
Metabolic Syndrome	Non-Obese	Total	0.00730 (0.00308, 0.01188)	0.73 (0.31, 1.19)	<0.001
		Direct	0.00760 (0.00340, 0.01215)	0.76 (0.34, 1.22)	<0.001
		Total Indirect	-0.00037 (-0.00054, -0.00024)	-0.04 (-0.05, -0.02)	<0.001
		Proportion Mediated	-0.05130 (-0.11976, -0.03017)	-5.13 (-11.98, -3.02)	<0.001
	Obese	Total	0.03419 (0.02988, 0.03809)	3.42 (2.99, 3.81)	<0.001
		Direct	0.03392 (0.02965, 0.03792)	3.39 (2.97, 3.79)	<0.001
		Total Indirect	0.00056 (0.00028, 0.00078)	0.06 (0.03, 0.08)	<0.001
		Proportion Mediated	0.01636 (0.00820, 0.02250)	1.64 (0.82, 2.25)	<0.001
Metabolic Syndrome and Cardiovascular Disease	Non-Obese	Total	0.03035 (0.02404, 0.03766)	3.04 (2.40, 3.77)	<0.001
		Direct	0.03045 (0.02407, 0.03779)	3.05 (2.41, 3.78)	<0.001
		Total Indirect	-0.00019 (-0.00071, 0.00011)	-0.02 (-0.07, 0.01)	0.18
		Proportion Mediated	-0.00635 (-0.02152, 0.00349)	-0.64 (-2.15, 0.35)	0.18
	Obese	Total	0.05647 (0.04920, 0.06370)	5.65 (4.92, 6.37)	<0.001
		Direct	0.05595 (0.04858, 0.06325)	5.60 (4.86, 6.33)	<0.001
		Total Indirect	0.00143 (0.00093, 0.00189)	0.14 (0.09, 0.19)	<0.001
		Proportion Mediated	0.02524 (0.01642, 0.03369)	2.52 (1.64, 3.37)	<0.001

Direct and indirect effects are reported against the control group Hypertension Only/Non-Obese. Outcome and mediator models were additionally adjusted for age, estimated glomerular filtration rate, sex, race, procedure type, ASA classification, smoking status, packed red blood cell transfusion, crystalloid equivalents given, >12 minutes of hypotension, nephrotoxic medication use, tranexamic acid use, year, and institution.

Appendix Table C.4b. Estimated direct effect of cardiometabolic latent class and indirect effects of general anesthesia as a mediator on the outcome of acute kidney injury

		Risk Difference (95% CI)	Risk Difference per 100 cases (95% CI)	P-Value
Metabolic Syndrome	Total	0.01243 (0.00909, 0.01573)	1.24 (0.91, 1.57)	<0.001
	Direct	0.01254 (0.00930, 0.01586)	1.25 (0.93, 1.59)	<0.001
	Total Indirect	-0.00015 (-0.00032, -0.00001)	-0.02 (-0.03, -0.00)	0.04
	Proportion Mediated	-0.01193 (-0.03011, -0.00048)	-1.19 (-3.01, -0.05)	0.04
Metabolic Syndrome and Cardiovascular Disease	Total	0.03470 (0.02965, 0.04063)	3.47 (2.97, 4.06)	<0.001
	Direct	0.03450 (0.02935, 0.04045)	3.45 (2.94, 4.05)	<0.001
	Total Indirect	0.00036 (0.00002, 0.00065)	0.04 (0.00, 0.07)	0.03
	Proportion Mediated	0.01033 (0.00073, 0.01918)	1.03 (0.07, 1.92)	0.03

Direct and indirect effects are reported against the control group Hypertension Only. Outcome and mediator models were additionally adjusted for age, estimated glomerular filtration rate, sex, race, obesity status, procedure type, ASA classification, smoking status, packed red blood cell transfusion, crystalloid equivalents given, >12 minutes of hypotension, nephrotoxic medication use, tranexamic acid use, year, and institution.

Appendix Table C.4c. Estimated direct effect of cardiometabolic latent class and indirect effects of general anesthesia as a mediator on the outcome of acute kidney injury

		Risk Difference (95% CI)	Risk Difference per 100 cases (95% CI)	P-Value
Obese	Total	0.02319 (0.02026, 0.02593)	2.32 (2.03, 2.59)	<0.001
	Direct	0.02266 (0.01982, 0.02539)	2.27 (1.98, 2.54)	<0.001
	Total Indirect	0.00082 (0.00054, 0.00098)	0.08 (0.05, 0.10)	<0.001
	Proportion Mediated	0.03551 (0.02306, 0.04151)	3.55 (2.31, 4.15)	<0.001

Direct and indirect effects are reported against the control group non-obese. Outcome and mediator models were additionally adjusted for age, estimated glomerular filtration rate, sex, race, cardiometabolic latent class, procedure type, ASA classification, smoking status, packed red blood cell transfusion, crystalloid equivalents given, >12 minutes of hypotension, nephrotoxic medication use, tranexamic acid use, year, and institution.

Appendix Table C.5a. Estimated direct effect of cardiometabolic latent class and indirect effects of >12 minutes of hypotension as a mediator on the outcome of acute kidney injury

		Risk Difference (95% CI)	Risk Difference per 100 cases (95% CI)	P-Value
Metabolic Syndrome	Total	0.01250 (0.00923, 0.01583)	1.25 (0.92, 1.58)	<0.001
	Direct	0.01256 (0.00931, 0.01587)	1.26 (0.93, 1.59)	<0.001
	Total Indirect	-0.00007 (-0.00016, -0.00002)	-0.01 (-0.02, -0.00)	0.01
	Proportion Mediated	-0.00557 (-0.01330, -0.00144)	-0.56 (-1.33, -0.14)	0.01
Metabolic Syndrome and Cardiovascular Disease	Total	0.03420 (0.02905, 0.04006)	3.42 (2.91, 4.01)	<0.001
	Direct	0.03428 (0.02910, 0.04017)	3.43 (2.91, 4.02)	<0.001
	Total Indirect	-0.00014 (-0.00032, -0.00004)	-0.01 (-0.03, -0.00)	0.01
	Proportion Mediated	-0.00416 (-0.00949, -0.00121)	-0.42 (-0.95, -0.12)	0.01

Direct and indirect effects are reported against the control group of Hypertension Only. Outcome and mediator models were additionally adjusted for age, estimated glomerular filtration rate, sex, race, procedure type, ASA classification, smoking status, general anesthesia use, packed red blood cell transfusion, crystalloid equivalents given, nephrotoxic medication use, tranexamic acid use, year, and institution.

Appendix Table C.5b. Estimated direct effect of cardiometabolic latent class and indirect effects of >12 minutes of hypotension as a mediator on the outcome of acute kidney injury

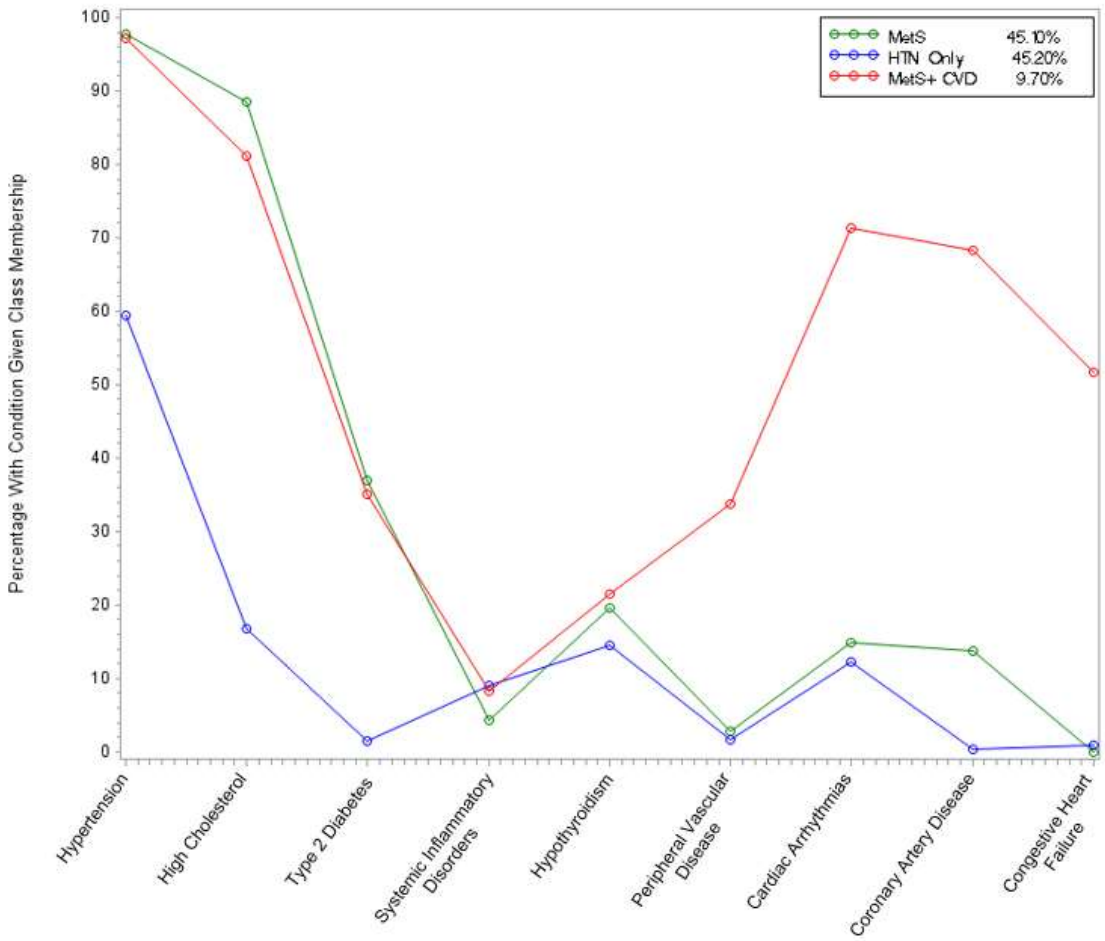
		Risk Difference (95% CI)	Risk Difference per 100 cases (95% CI)	P-Value
Obese	Total	0.02247 (0.01967, 0.02518)	2.25 (1.97, 2.52)	<0.001
	Direct	0.02246 (0.01967, 0.02511)	2.25 (1.97, 2.51)	<0.001
	Total Indirect	-0.00007 (-0.00020, -0.00001)	-0.01 (-0.02, -0.00)	0.04
	Proportion Mediated	-0.00322 (-0.00839, -0.00032)	-0.32 (-0.84, -0.03)	0.04

Direct and indirect effects are reported against the control group of non-obese. Outcome and mediator models were additionally adjusted for age, estimated glomerular filtration rate, sex, race, procedure type, ASA classification, smoking status, general anesthesia use, packed red blood cell transfusion, crystalloid equivalents given, nephrotoxic medication use, tranexamic acid use, year, and institution. There was a statistically significant interaction between exposure and mediator, which is reflected in the model construction.

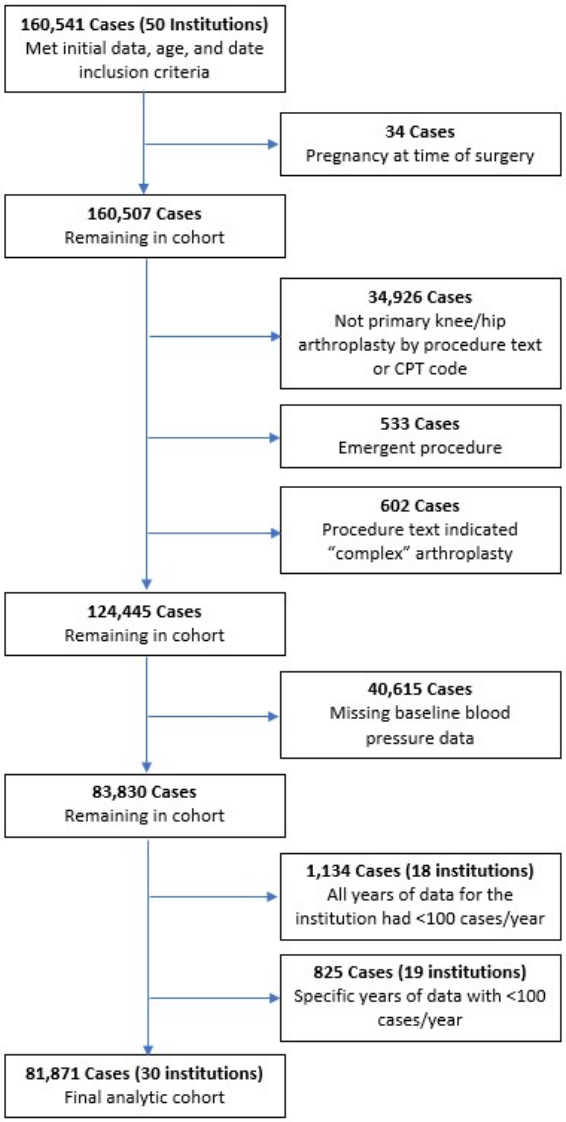
Appendix Table C.5c. Estimated direct effect of cardiometabolic latent class with/without obesity and indirect effects of general anesthesia as a mediator on the outcome of acute kidney injury

			Risk Difference (95% CI)	Risk Difference per 100 cases (95% CI)	P-Value
Hypertension Only	Obese	Total	0.01743 (0.01354, 0.02114)	1.74 (1.35, 2.11)	<0.001
		Direct	0.01728 (0.01336, 0.02110)	1.73 (1.34, 2.11)	<0.001
		Total Indirect	-0.00027 (-0.00055, -0.00007)	-0.03 (-0.06, -0.01)	<0.001
		Proportion Mediated	-0.01559 (-0.03291, -0.00382)	-1.56 (-3.29, -0.38)	<0.001
Metabolic Syndrome	Non-Obese	Total	0.00740 (0.00323, 0.01196)	0.74 (0.32, 1.20)	<0.001
		Direct	0.00720 (0.00297, 0.01188)	0.72 (0.30, 1.19)	<0.001
		Total Indirect	-0.00015 (-0.00045, 0.00007)	-0.02 (-0.05, 0.01)	0.18
		Proportion Mediated	-0.01962 (-0.07667, 0.00957)	-1.96 (-7.67, 0.96)	0.18
	Obese	Total	0.03345 (0.02919, 0.03762)	3.35 (2.92, 3.76)	<0.001
		Direct	0.03331 (0.02906, 0.03750)	3.33 (2.91, 3.75)	<0.001
		Total Indirect	-0.00025 (-0.00051, -0.00008)	-0.03 (-0.05, -0.01)	0.01
		Proportion Mediated	-0.00761 (-0.01524, -0.00237)	-0.76 (-1.52, -0.24)	0.01
Metabolic Syndrome and Cardiovascular Disease	Non-Obese	Total	0.03023 (0.02340, 0.03727)	3.02 (2.34, 3.73)	<0.001
		Direct	0.03004 (0.02332, 0.03713)	3.00 (2.33, 3.71)	<0.001
		Total Indirect	-0.00005 (-0.00055, 0.00060)	-0.01 (-0.06, 0.06)	0.96
		Proportion Mediated	-0.00164 (-0.01981, 0.02083)	-0.16 (-1.98, 2.08)	0.96
	Obese	Total	0.05460 (0.04739, 0.06184)	5.46 (4.74, 6.18)	<0.001
		Direct	0.05439 (0.04715, 0.06164)	5.44 (4.72, 6.16)	<0.001
		Total Indirect	-0.00002 (-0.00057, 0.00061)	-0.00 (-0.06, 0.06)	0.85
		Proportion Mediated	-0.00045 (-0.01042, 0.01110)	-0.05 (-1.04, 1.11)	0.85

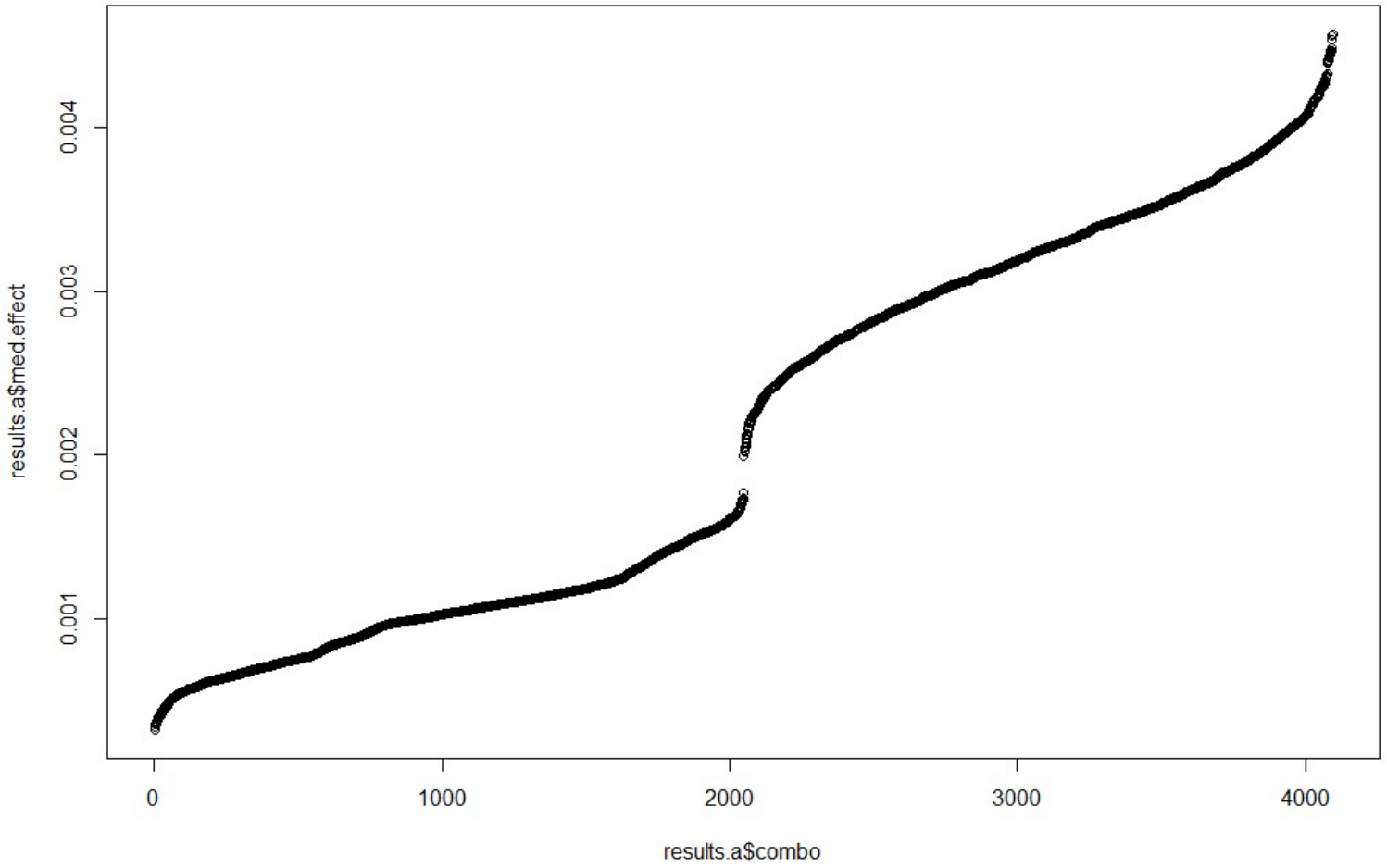
Direct and indirect effects are reported against the control group of Hypertension Only/Non-obese. Outcome and mediator models were additionally adjusted for age, estimated glomerular filtration rate, sex, race, procedure type, ASA classification, smoking status, general anesthesia use, packed red blood cell transfusion, crystalloid equivalents given, nephrotoxic medication use, tranexamic acid use, year, and institution. There was a statistically significant interaction between exposure and mediator, which is reflected in the model construction.



Appendix Figure C.1. Percentage of cases with a cardiometabolic condition given class membership for the three-class latent class model. The three-class model consisted of: one class with moderate probability of hypertension ("HTN Only"; n = 37,032), one class with high probability of high cholesterol and hypertension and moderate probability of diabetes ("MetS", n = 36,889), and one class with high probability of hypertension, high cholesterol, cardiac arrhythmias, coronary artery disease (CAD), and congestive heart failure (CHF), and moderate probability of diabetes and peripheral vascular disease ("MetS+CVD"; n = 7,950). Abbreviations: MetS – Metabolic Syndrome, HTN – Hypertension, CVD – Cardiovascular Disease



Appendix Figure C.2. Study patient flow chart



Appendix Figure C.3. Sensitivity analyses of all possible covariate combinations on the mediation effect of general anesthesia on the relationship between the "Metabolic Syndrome + Cardiovascular Disease"/Obese class and the outcome of AKI (reference "Hypertension Only"/Non-obese). Data are ordered by effect size.

Chapter 4

Polygenic Risk Scores for Cardiometabolic Disorders and Association with Postoperative Acute Kidney Injury

4.1. Abstract

Introduction: In addition to phenotypic risk factors, many studies have examined genetic risk factors for acute kidney injury (AKI) in both the perioperative and critical care settings. Genes shown in these studies to have strong positive associations with AKI include those related to blood pressure, and insulin resistance and inflammation. Given the suggested associations between genes related to phenotypic cardiometabolic risk factors for AKI, as well as AKI itself, this study aimed to examine the association between polygenic risk scores for type 2 diabetes, coronary artery disease, and BMI and postoperative AKI.

Methods: All non-pregnant patients ≥18 years of age with genetic data available in the Michigan Genomics Initiative presenting to the University of Michigan for a non-cardiac, non-renal, non-urologic, and non-liver transplant procedure from January 1, 2014 to December 31, 2019 were eligible for study inclusion. Genetic data from this study were taken from the Michigan Genomics Initiative Data Freeze 4, which comprised 60,215 genotyped participants. Polygenic risk scores (PRS) were generated for type 2 diabetes (PRS_{T2D}), coronary artery disease (PRS_{CAD}), and BMI (PRS_{BMI}) using previously published weights (pgscatalog.org). Calculated PRS were binned into deciles. Logistic regression models containing preoperative and intraoperative data

were run separately with AKI as the outcome, defined using Kidney Disease – Improving Global Outcomes (KDIGO) criteria, and PRS as the exposure of interest.

Results: A total of 14,824 unique patients were included in our analytic cohort (737 with AKI). Patients with AKI had a higher prevalence of hypertension, peripheral vascular disorders, diabetes, cardiac arrhythmias, coronary artery disease, congestive heart failure, and obesity. After adjustment for preoperative factors, those with type 2 diabetes had 1.55 times the odds of AKI than those without type 2 diabetes (95%CI: 1.31, 1.82). This effect was slightly attenuated after additional adjustment for intraoperative characteristics (adjusted odds ratio (AOR) 1.52, 95%CI: 1.28, 1.80). Compared to those in the lowest decile of the PRS_{T2D} from Mars, et al. 2020, those in the highest decile had 1.46 times the odds of AKI after adjustment for preoperative factors (95%CI: 1.04, 2.06). This effect was attenuated in the intraoperative model, but remained statistically significant (AOR 1.43, 95%CI: 1.00, 2.05). No other statistically significant effects were seen for other PRS. However, model area under the curve values remained largely consistent between phenotype and PRS models.

Conclusion: In this single-center cohort of non-cardiac, non-renal, non-urologic, and non-liver transplant procedures we found little evidence of a clinically significant effect of polygenic risk for type 2 diabetes, coronary artery disease, or BMI on the risk of post-operative acute kidney injury. However, there was little difference in population-level model predictive capability when the polygenic risk scores were used in place of the phenotype, indicating the potential research utility of these scores in datasets where granular phenotypes for these complex conditions are not available.

4.2. Background

Acute kidney injury (AKI) is a major postoperative complication following both cardiac and non-cardiac surgeries, and is associated with an increased hospital length of stay and postoperative mortality[84]. Even those with mild or subclinical AKI following surgery can have lasting health consequences including permanent kidney damage and an increased mortality risk[84]. However, treatment for AKI is largely supportive rather than curative, making identification of those at higher risk imperative[14,84].

A number of single- and multi-center studies of the non-cardiac surgical population have shown comorbidities such as hypertension, diabetes, and high body mass index to be independent predictors of AKI through traditional modeling strategies[8,17-21]. In addition to these phenotypic risk factors, many studies have examined genetic risk factors for AKI in both the perioperative and critical care settings[92]. Variants and polymorphisms of genes shown in these studies to have strong positive associations with AKI include those related to blood pressure[136,137], and insulin resistance and inflammation[136,138]. A systematic review of genetic risk of AKI either showed no association or a positive association with a lower quality review score, with mixed significance across studies[92]. Other studies have found that insertion/deletion polymorphisms in the *ACE* gene (related to blood pressure regulation[139]) and isoforms of *APO E* (related to metabolism of fats[90]), as well as the T-786C polymorphism in *eNOS* (related to vascular tone[91]), are associated with increased risk of AKI and poor renal function in cardiac patients, though there have been contradictory findings regarding the role of inflammation-related and other genetic variants in the development of acute kidney injury[92-96]. To date, there is no published polygenic risk score for AKI; given the complex nature of the condition, a polygenic score would more fully capture genetic risk than candidate genes alone.

Given the suggested associations between genes related to phenotypic cardiometabolic risk factors for AKI and the outcome, this study aimed to examine the association between polygenic risk scores for type 2 diabetes, coronary artery disease, and BMI and postoperative AKI. We hypothesized that polygenic risk scores for these conditions would be associated with increased odds of AKI after adjustment for other comorbidities. Additionally, we hypothesized that inclusion of PRS would increase the predictive capability over a clinical model alone.

4.3. Methods

All patients ≥18 years of age with genetic data available in the Michigan Genomics Initiative presenting to the University of Michigan for a non-cardiac, non-renal, non-urologic, and non-liver transplant procedure from January 1, 2014 to December 31, 2019 were eligible for study inclusion (Appendix Table D.1). Those individuals without both preoperative and postoperative creatinine data, missing any ICD codes, with preoperative renal failure, those with an ASA class of 5 or 6, and those who were pregnant or receiving a labor and delivery procedure were excluded. To avoid upweighting the polygenic scores of individuals with multiple surgical cases, only the first case meeting all inclusion criteria was included in the analysis. This retrospective observational study was approved by the Institutional Review Board at our institution with a waiver of informed consent (HUM00180435). This cohort has been partially analyzed previously as part of a multi-center study examining the outcome of AKI[14].

Primary Outcome

The primary outcome was acute kidney injury (AKI). The criteria for this outcome are adapted from the validated Kidney Disease – Improving Global Outcomes (KDIGO) definition, which is a globally accepted standard for defining acute kidney injury[116]. For the purposes of this study, the outcome of AKI will be defined as any KDIGO stage ≥1[14]; a postoperative creatinine

within 7 days ≥ 1.5 times the baseline creatinine or the postoperative creatinine within 48 hours of anesthesia end ≥ 0.3 mg/dL above the baseline creatinine.

Exposure of Interest

Genome-wide genetic data from this study were taken from the Michigan Genomics Initiative Data Freeze 4, which comprised 60,215 genotyped participants[140]. Approximately 570,000 genotypes were assayed for each participant using custom arrays based on the Illumina Infinium CoreExome 24 v1.0, v1.1, or v1.3 bead arrays. Further genotypes being imputed using the Haplotype Reference Consortium r1.1 and mapped to build 37 of the human genome. Data were filtered post-imputation to remove variants with poor imputation quality (Rsq < 0.3) and rare variants (minor allele frequency <0.01%). Following filtering, the genetic data for participants contained 32,401,123 variants. The majority ancestry of participants was inferred using the ADMIXTURE software[141]. Our analysis considers only those of majority European ancestry, defined as genotype-inferred majority ancestry using the ADMIXTURE software, encompassing the majority of MGI participants (88.1%).

Polygenic risk scores (PRS) were generated for type 2 diabetes (PRS_{T2D}), coronary artery disease (PRS_{CAD}), and BMI (PRS_{BMI}) using previously published weights (pgscatalog.org). Scores were computed on the filtered genetic data using the PLINK (v2.0) software[142]. In general, to be considered a potential polygenic risk score, the study had to demonstrate the following: use of a large external GWAS, utilizing a score creation methodology which accounts for linkage disequilibrium, score derivation in a European-only cohort, published weights on the GRCh37 or hg19 builds, and be published in a peer-reviewed journal. Information regarding the selected polygenic score weights can be found in Appendix Table D.2.

Of the 36 potential polygenic scores for type 2 diabetes available on the PGS Catalog (accessed on March 13, 2022), 33 were excluded from consideration due to not accounting for linkage disequilibrium in score creation (n=24), unclear GWAS origins (n=2), using HbA1c to define controls (n=1), pre-print (n=2), using a different genome build (n=3) and low comparative AUC in derivation cohort (n=1). The three polygenic scoring weights considered for this analysis were from Khera[143] (https://www.pgscatalog.org/score/PGS000014/), Mars[144] (https://www.pgscatalog.org/score/PGS000330/), and Mahajan[145] (https://www.pgscatalog.org/score/PGS000036/).

Of the 28 potential polygenic scores for coronary artery disease available on the PGS Catalog, 26 were excluded from consideration due to not accounting for linkage disequilibrium in score creation (n=15), deriving the score in a non-European or multiethnic cohort (n=4), using a derivation cohort with <500 cases (n=2), using a different genome build (n=1), pre-print (n=1), and being developed for a phenotype of coronary atherosclerosis (n=2). The two polygenic scoring weights considered for this analysis were from Khera[143] (https://www.pgscatalog.org/score/PGS000013/) and Mars[144] (https://www.pgscatalog.org/score/PGS000329/).

Of the 18 potential polygenic scores for BMI available on the PGS Catalog, 17 were excluded from consideration due to not accounting for linkage disequilibrium in score creation (n=7), small derivation cohort (n=1), reference allele not included (n=1), sex-specific scores (n=2), pre-prints (n=2), related phenotype but not scoring for BMI (n=3), and no use of an external genome-wide association study (n=1). The remaining polygenic scoring weight considered was from Khera[146] (https://www.pgscatalog.org/score/PGS000027/).

Final polygenic risk scores were tested in our cohort by running a series of models against the outcome of the phenotype of interest. Model 1 contained the unadjusted association between the phenotype and polygenic risk score (per 1SD increase). An additional adjusted model was run for each, accounting for age and BMI at the time of procedure, genetic-inferred sex, and the top 10 genetic principal components (Appendix Table D.3). Following within-cohort validation, the Khera PRS_{T2D} was removed from further consideration due to the lower AUC compared to the other PRS_{T2D}.

To facilitate interpretation, each PRS was standardized to a mean of 0 and a standard deviation of 1 given the normal distribution of the score. Data were grouped into deciles; the decile variable was modeled as either continuous, or as a 3-level categorical variable (1^{st} decile – reference, 2^{nd}-9^{th} decile, 10^{th} decile).

Cardiometabolic Disease Phenotypes

All comorbidities were defined based on ICD 9/10 codes (including codes present on admission), relevant history and physical (H&P) elements, and preoperative laboratory or physiologic measurements, as appropriate. Definitions of each element are in Appendix Table D.4. Patients meeting any of the criteria for a given condition were coded as "yes" for that condition.

Other Covariates

Additional variables taken at time of surgery considered in analyses included age, sex, preoperative estimated glomerular filtration rate (eGFR), smoking status, year of case, and American Society of Anesthesiologists (ASA) physical status. ASA physical status is an overall physician assessment of patient health where a class of 1 indicates a healthy patient and a class of 4 indicates life-threatening severe systemic disease[117]. Intraoperative data collected included

use of general anesthesia (yes/no), blood transfusions (yes/no), total fluid volume given, use of nephrotoxic medications (yes/no, use of non-steroidal anti-inflammatory medications, antibiotics, or diuretics), use of tranexamic acid (yes/no) and intraoperative hypotension defined as the number of minutes with mean arterial pressure <65 mmHg[14]. Year is treated as a categorical variable.

Statistical Analysis

Descriptive statistics were presented as frequencies with percentages for categorical variables and either means with standard deviations or medians with interquartile ranges for continuous variables, as appropriate. Continuous data was assessed for normality using histograms, the Kolmogorov-Smirnov test, and Q-Q plots. Univariate comparisons between those with and without AKI were computed using chi-squared or Fisher's exact tests for categorical variables and either independent t-tests or Wilcoxon rank-sum tests for continuous variables, as appropriate. A p-value of 0.05 was considered statistically significant, and SAS will be used for all analyses. Prediction accuracy was assessed using the area under the receiver operating curve (AUC).

Prior to multivariable model construction, collinearity was assessed using variance inflation factor (VIF) and correlations. A VIF >=10 or correlation >= 0.7 indicated significant multicollinearity between variables. Given the known associations between cardiometabolic conditions such as type 2 diabetes and clinical sequelae such as peripheral vascular disease, additional associations were assessed for these variables using crosstabs, with a column and row percentages in the yes/yes square >70% indicating potential significant collinearity. Variables were selected for potential model inclusion based on univariate statistical significance and, in the presence of collinearity, unadjusted effect size for the outcome of AKI.

Variables selected a priori for inclusion in all preoperative models included age (<50 vs. ≥50), sex, eGFR, ASA class (<3 vs ≥3), and continuous polygenic risk score decile. Cardiometabolic comorbidities were entered sequentially into the model individually and in combination, and the model with the lowest AIC value was selected. For the type 2 diabetes models, the following conditions were considered: hypertension, peripheral vascular disease (PVD), congestive heart failure, and coronary artery disease (CAD). The final model selected contained hypertension, peripheral vascular disease, congestive heart failure (CHF). For the CAD models, the following conditions were considered: hypertension, PVD, type 2 diabetes, and CHF. All four remained in the final model.

Variables selected for inclusion in the intraoperative models included all preoperative variables, case duration (<2 hours, 2-4 hours, >4 hours), general anesthesia use, fluid volume (per 500mL crystalloid equivalents), packed red blood cell transfusion, minutes of hypotension >75th percentile (yes/no), year, major procedure based on ASA base units (yes/no), and anesthesia CPT code body location group.

Preoperative and intraoperative models were run for all PRS of interest, separately for continuous and categorical decile, with the outcome of AKI. An additional set of models was run with the phenotype of diabetes or CAD, respectively, in place of the PRS. A final model was constructed with both the diabetes and CAD PRS. To assess sub-populations where the PRS might be more predictive of AKI risk, a series of secondary analyses were conducted for the following populations: age <50 and age ≥ 50, diabetes and obesity groups for diabetes PRS (no diabetes/no obesity, obesity without diabetes, diabetes without obesity, yes diabetes/yes obesity), and CAD and obesity groups for CAD PRS (no CAD/no obesity, obesity without CAD, CAD without obesity, yes CAD/yes obesity).

Additional analyses were conducted to determine if the effect of phenotype/PRS mismatch was predictive of AKI risk. Specifically, for each PRS of interest, those with the lowest decile with phenotype were compared to those in the highest decile without the phenotype. Statistically significant univariate associations were assessed with similar models as above.

Power Calculation

An *a priori* power calculation was conducted. Based on preliminary aggregate data from MGI Freeze 2, the outcome rate is approximately 6.8%. Assuming an alpha of 0.05 and an AKI outcome rate of 6% at the mean PRS, a sample size of 31,609 would provide 95% power to detect an odds ratio of 1.09 for a 1 standard deviation increase in the PRS. This corresponds to an increase in proportion of outcome from 6% at the mean to 6.5% one standard deviation above the mean.

4.4. Results

Of the 376,203 adult cases conducted at Michigan Medicine between 1/1/2014 and 12/31/2019, 91,895 met all inclusion criteria (Figure 4.1). Of these, an additional 66,204 cases were excluded due to not having genetic data and 2,091 cases were excluded for being of non-European majority ancestry. Compared to those without genetic data available in MGI in Freeze 4, those cases in MGI were generally younger and healthier, and more likely to be undergoing a major procedure (Appendix Table D.5). There were no significant differences in BMI, sex, cardiometabolic comorbidities, anesthesia type, or outcome rate between these groups.

The remaining 23,600 surgical cases represented 14,824 unique patients, with an overall AKI rate of 4.97% (737 patients). Compared to those without AKI, those with AKI were older and more frequently male, with a higher BMI and ASA physical classification scores (Table 4.1).

Patients with AKI had a higher prevalence of hypertension, peripheral vascular disorders, diabetes, cardiac arrhythmias, coronary artery disease, congestive heart failure, and obesity.

Polygenic Risk Scores

Polygenic risk scores for all conditions were normally distributed. There was a marked increase in prevalence of all phenotypes with corresponding PRS as decile increased (Figure 4.2). A majority of variants from the selected PRS weighting files were included in the score calculation in our dataset, ranging from 93.98% (Khera PRS_{T2D}) to 99.28% (Mahajan PRS_{T2D}) (Appendix Figure D.1). Mahajan PRS_{T2D} decile and Mars PRS_{T2D} decile were modestly correlated at the individual level ($\rho = 0.606$). Likewise, Mars PRS_{CAD} decile and Khera PRS_{CAD} decile were modestly correlated at the individual level, with a weaker effect size ($\rho = 0.496$).

Type 2 Diabetes

Without adjustment for covariates, those with the type 2 diabetes phenotype had 2.20 times the odds of AKI than those without type 2 diabetes (95%CI: 1.89, 2.57). After adjustment for preoperative factors, this effect was attenuated to 1.55 times the odds of AKI compared to those without type 2 diabetes (95%CI: 1.31, 1.82). The association was further attenuated but remained statistically significant after additional adjustment for intraoperative characteristics (adjusted odds ratio (AOR) 1.52, 95%CI: 1.28, 1.80). The relationship between the continuous decile of Mars PRS_{T2D} and AKI was not statistically significant in either the preoperative or intraoperative models (Figure 4.3, Appendix Figure D.2). The AUC was slightly lower in the Mars PRS_{T2D} model as compared to the phenotype model (preoperative: 0.666 and 0.674, intraoperative: 0.781 and 0.785, respectively). These results remained consistent across subgroups. Similar results were seen for continuous decile of Mahajan PRS_{T2D}.

Compared to those in the lowest decile of Mars PRS_{T2D}, those in the highest decile had 1.46 times the odds of AKI after adjustment for preoperative factors (95%CI: 1.04, 2.06; Figure 4.3). This effect was attenuated in the intraoperative model, but remained statistically significant (AOR 1.43, 95%CI: 1.00, 2.05). However, there were no statistically significant differences in subgroup analyses, or within the categories of Mahajan PRS_{T2D}.

Notably, the model AUC was consistently higher for the no diabetes/no obesity and age <50 subgroups compared to the other subgroups for both PRS_{T2D} (Appendix Table D.6).

Coronary Artery Disease

Without adjustment for covariates, those with the phenotype for coronary artery disease had 2.00 times the odds of AKI as compared to those without coronary artery disease (95%CI: 1.69, 2.37). However, after adjustment for preoperative factors, the difference in odds of AKI between those with and without the CAD phenotype was not statistically significant (AOR 1.03, 95%CI: 0.85, 1.25). Likewise, there were no statistically significant associations between continuous decile of the Khera PRS_{CAD} or Mars PRS_{CAD} (Figure 4.4). The AUC for the phenotype and PRS_{CAD} models were identical (preoperative: 0.674, intraoperative: 0.785 for all).

There were no statistically significant differences in odds of AKI for the comparison of highest to lowest PRS decile for either Khera PRS_{CAD} or Mars PRS_{CAD} (Figure 4.4). Within the subgroup of age ≥ 50, those in the highest Mars PRS_{CAD} decile had 1.52 times the odds of AKI compared to those in the lowest decile (95%CI: 1.04, 2.22); however, this same association was not seen for Khera PRS_{CAD} within this subgroup.

Notably, the model AUC was consistently higher for the no CAD/no obesity and age <50 subgroups compared to the other subgroups for both PRS_{CAD} (Appendix Table D.5).

BMI

Without adjustment for covariates, those with the phenotype for obesity had 1.20 times the odds of AKI compared to those without obesity (95%CI: 1.03, 1.39). After adjustment for preoperative factors, there was no statistically significant difference in odds of AKI between those with and without the obesity phenotype (AOR 0.97, 95%CI: 0.83, 1.12). Likewise, there were no statistically significant associations between continuous decile of the Khera PRS_{BMI} (Figure 4.5). There were no differences in the model AUC between phenotype and PRS_{BMI} models (preoperative: 0.674, intraoperative: 0.785 for all). There were no statistically significant differences in odds of AKI for the three-level PRS variable. Similar to PRS_{T2D} and PRS_{CAD}, the model AUC was higher for those in the age <50 subgroup for both preoperative and intraoperative models (Appendix Table D.5).

Multivariable Model with All PRS

A multivariable model was constructed containing three PRS: Mars PRS_{T2D}, Khera PRS_{CAD}, and Khera PRS_{BMI}. There were no statistically significant effects of continuous decile of PRS in the preoperative or intraoperative models. However, after adjusting for preoperative factors and the other PRS, those in the highest decile of Mars PRS_{T2D} had 1.48 times the odds of AKI compared to those in the lowest decile (95%CI: 1.04, 2.11). This effect was minimally attenuated in the intraoperative model (data not shown).

Secondary Analysis

A secondary analysis was conducted comparing those in the highest decile without the phenotype compared to the lowest decile with the given phenotype. For PRS_{T2D}, there were significantly more individuals in the highest PRS decile without diabetes than the lowest decile with diabetes (Mars PRS_{T2D}: 873 (85.8%) vs. 144 (14.2%), Mahajan PRS_{T2D}: 747 (82.8%) vs. 155 (17.2%)). Similar results were seen for PRS_{CAD} (Khera PRS_{CAD}: 1205 (88.3%) vs. 160

(11.7%), Mars PRS_{CAD}: 1174 (86.5%) vs. 184 (13.6%)). There was an even distribution between groups for Khera PRS_{BMI} (451 (48.9%) vs. 472 (51.1%)). There were no statistically significant univariate associations between sensitivity group membership and AKI, with the exception of Mahajan PRS_{T2D} (unadjusted OR for those in the lowest decile with phenotype: 2.86, 95%CI: 1.48, 5.51). This effect was attenuated but remained statistically significant after adjustment for intraoperative variables (AOR: 2.24, 95%CI: 1.14, 4.38), suggesting the phenotypic effect itself is stronger on risk of AKI than genotypic risk for the phenotype (data not shown).

4.5. Discussion

In this single-center cohort of non-cardiac, non-renal, non-urologic, and non-liver transplant procedures we found limited evidence for an association between polygenic risk for type 2 diabetes, coronary artery disease, or BMI and the risk of post-operative acute kidney injury. This suggests that the risk for AKI conferred by these conditions may be due to a mechanical mechanism of action rather than shared genetic risk. However, there was little difference in population-level model predictive capability when the polygenic risk scores were used in place of the phenotype, indicating the potential research utility of these scores in datasets where clinical measurements or diagnoses of phenotypes are not available, or where the phenotype may not yet have occurred.

Our rationale for examining PRS for cardiometabolic conditions rather than for AKI itself was twofold. First, the conditions of interest develop gradually over time, with subclinical changes occurring to underlying structures prior to disease diagnosis; there is therefore potential for high polygenic risk scores to serve as a proxy measure for subclinical or undiagnosed disease for some individuals. Second, clean and robust phenotypes for complex conditions such as type 2 diabetes and coronary artery disease may not be available in many cohorts with genetic data,

which often are not linked to electronic health records or International Classification of Disease (ICD) classification codes for determining phenotype.

Those in the highest decile of the Mars PRS_{T2D} showed 1.46 times increased odds of AKI compared to those in the lowest decile. Notably, this effect is only 5.8% attenuated from that of the type 2 diabetes phenotype and remained fairly stable after adjustment for intraoperative factors. The rate of type 2 diabetes in the highest PRS_{T2D} decile was 42.4% vs. 9.8% in the lowest decile. Given the high rate of the diabetic phenotype in the highest decile of the Mars PRS_{T2D} and the significant adjusted association between diabetes phenotype and AKI, these results are not surprising. Although the Mahajan PRS_{T2D} was not statistically significant, effect sizes trended similarly, suggesting that there is potential for a clinically meaningful effect of high PRS_{T2D} on risk of AKI and utilization as a proxy measure for the phenotype. Significant variation in magnitude and direction of adjusted effects within subgroups may be artificial due to the lack of statistical power to make inferences regarding these subpopulations.

Many studies have found diabetes to be associated with AKI, though the exact mechanism of action is unknown. It has been hypothesized that the increased risk of AKI is related to vascular damage from a hyperglycemic and hyper-inflammatory state, and in more severe cases of diabetes may also be related to atherosclerosis changes within the kidney which would reduce functionality[88]. The results of our sensitivity analysis seem to potentially support that the phenotypic risk alone is stronger than the polygenic risk alone, as those with low Mahajan PRS_{T2D} and diabetes phenotype had 2.2 times the odds of AKI after adjustment for intraoperative factors than those with high Mahajan PRS_{T2D} without diabetes. It is possible that PRS for conditions closer to the hypothesized mechanisms, such as inflammation or glucose metabolism and insulin resistance, might be more strongly predictive of AKI.

There was additionally a minimal effect of PRS_{CAD} on the risk of AKI regardless of cohort or scores examined. After adjustment there were also no statistically significant associations between CAD phenotype and the outcome in our cohort. It is therefore not surprising that there was no association seen between PRS_{CAD} and risk of AKI. The results of PRS_{BMI} and the phenotype were similarly non-significant after adjustment. This lack of an adjusted effect may be due to confounding from other cardiometabolic factors included in the models such as type 2 diabetes and peripheral vascular disease, both risk factors for CAD[147] and potential consequences of obesity[50,54].

It is important to note that despite few statistically significant results, there were minimal changes in population-level model area under the curve between the phenotype models and those including PRS. Additionally, model coefficients for other factors remained constant across both phenotype and PRS models indicating the other effects were not differentially influenced by comorbidity definition (data not shown). Together, this indicates there is potential utility of these polygenic scores for use as a covariate when measured phenotypes are not available for these complex conditions. While such a use would be fairly novel, it could allow for more dynamic analyses of outcomes in genetic cohorts with limited phenotyping, especially of cardiometabolic sequelae like myocardial infarction or stroke. Future work is needed to determine if there are particular sub-populations or conditions for which this use is most appropriate.

This study has several strengths, most notably the large sample size of a general surgical cohort, allowing for the robust examination of polygenic risk scores in relation to a fairly rare postoperative event. Additionally, the large European ancestry population within the MGI dataset allowed for a more robust selection of potential polygenic risk scores for use within our analytic cohort; a vast majority of publish PRS for these conditions have been derived and

validated in those of European ancestry. The most notable limitation of the study is lack of generalizability to surgical patients such as those receiving cardiac surgery. Our study criteria excluded cardiac surgery patients from this analysis because of difficulties in isolating the contribution of the PRS on AKI given strong physiologic risk of AKI conferred by the procedure itself. However, cardiac surgery cohorts likely have greater phenotypic and genetic risk for conditions such as type 2 diabetes and coronary artery disease, a direct precursor to many of these procedures, and thus higher rates of AKI. Future studies with larger available sample sizes may be better equipped to disentangle these relationships, including the exploration of potential mediation by surgical processes such as use of cardiopulmonary bypass, which significantly alter hemodynamics for the duration of the procedure[148]. Another limitation is that our selected polygenic risk scores did not reflect risk for physiologic processes such as inflammation, which may be more predictive of AKI; the physiologic data for such PRS were not available in our analytic cohort. However, this research has provided a first step in examining the complex relationship between diseases with a highly inflammatory process, such as type 2 diabetes, and AKI.

4.6. Conclusion

In this single-center cohort of non-cardiac, non-renal, non-urologic, and non-liver transplant procedures we found little evidence of a clinically significant effect of polygenic risk for type 2 diabetes, coronary artery disease, or BMI on the risk of post-operative acute kidney injury. However, there was little difference in population-level model predictive capability when the polygenic risk scores were used in place of the phenotype, indicating the potential utility of these scores in datasets where granular phenotypes for these complex conditions are not available , or where the phenotype may not yet have occurred.

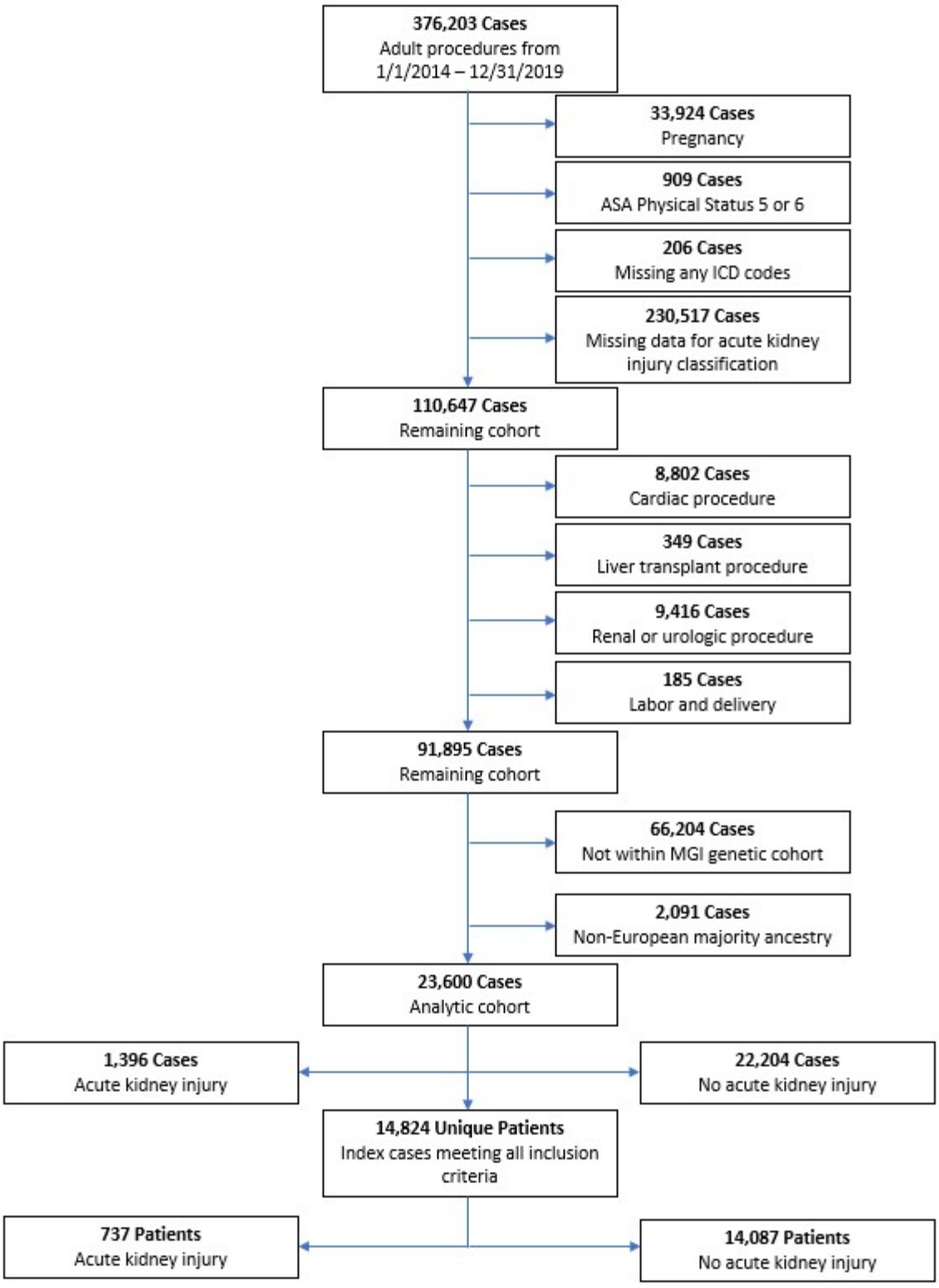
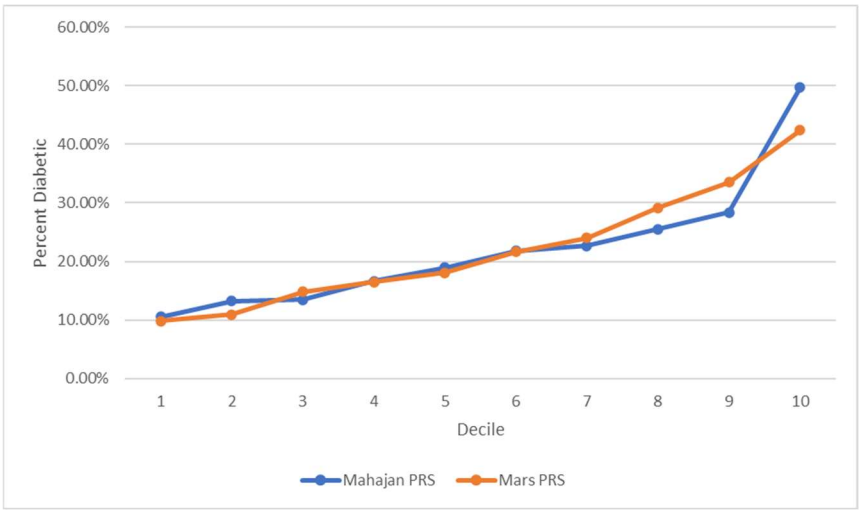


Figure 4.1. Patient inclusion and exclusion flow diagram. Unless otherwise stated, the numbers listed are at the case level, and individuals may have multiple cases represented in the data.

A.



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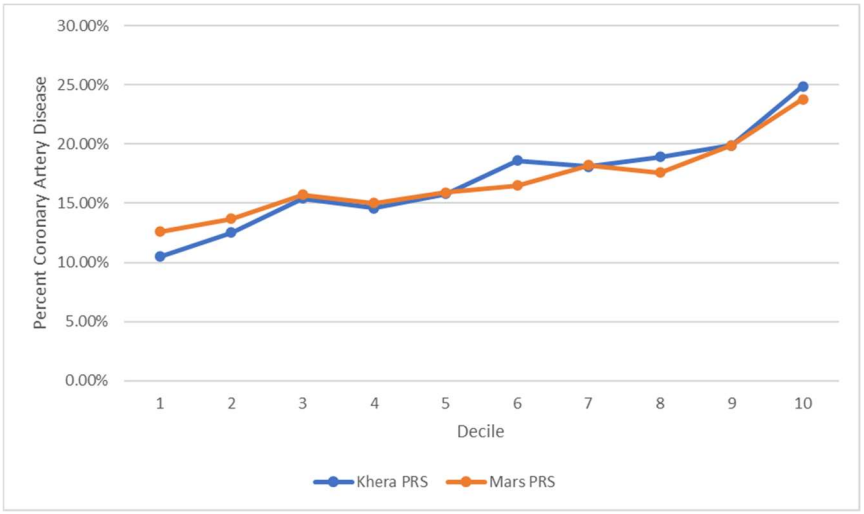

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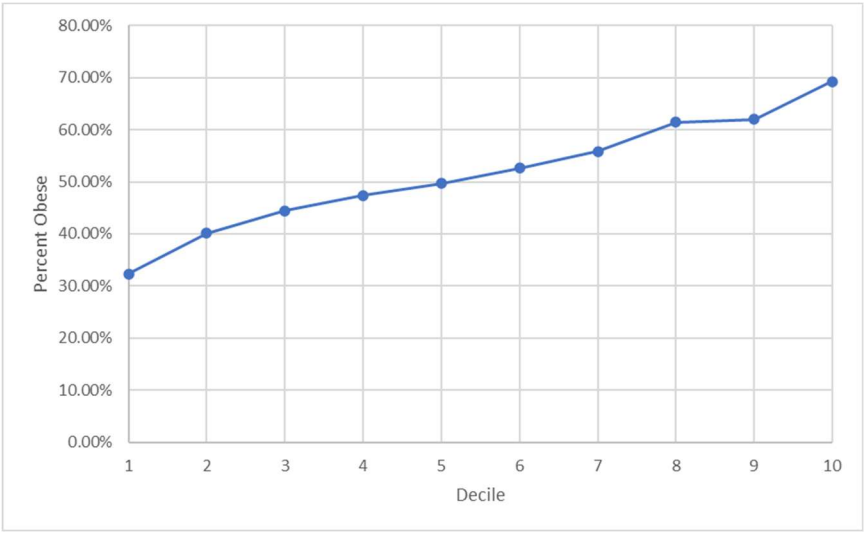


Figure 4.2. Trends of phenotype presentation by decile of polygenic risk score for (A) PRS_{T2D}, (B) PRS_{CAD}, and (C) Khera PRS_{BMI}.

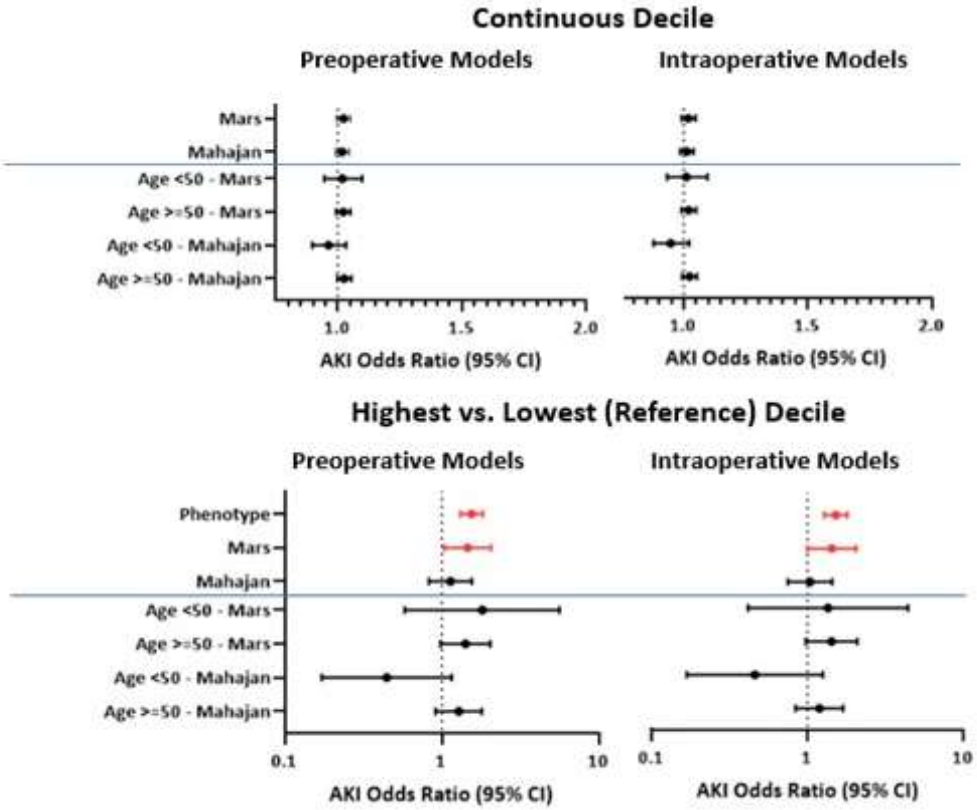


Figure 4.3. Forest plots of adjusted odd of acute kidney injury (AKI) for models containing type 2 diabetes polygenic risk scores. Preoperative models were adjusted for age ≥ 50, sex, ASA status ≥ 3, estimated glomerular filtration rate, hypertension, congestive heart failure, peripheral vascular disease. Intraoperative models were adjusted for preoperative factors, case duration, general anesthesia, fluid volume, packed red blood cell transfusion, minutes of hypotension ≥75th percentile, year, major procedure, and anesthesia current procedure terminology code body location.

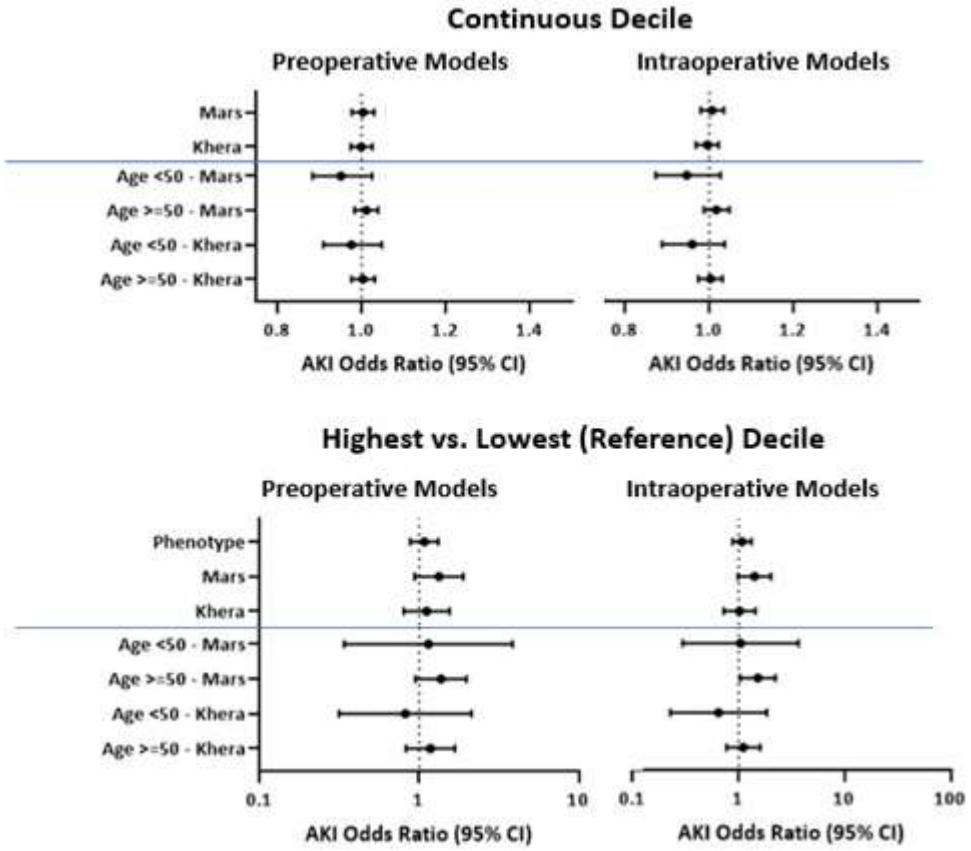


Figure 4.4. Forest plots of adjusted odd of acute kidney injury (AKI) for models containing coronary artery disease polygenic risk scores. Preoperative models were adjusted for age ≥ 50, sex, ASA status ≥ 3, estimated glomerular filtration rate, hypertension, congestive heart failure, peripheral vascular disease, and type 2 diabetes. Intraoperative models were adjusted for preoperative factors, case duration, general anesthesia, fluid volume, packed red blood cell transfusion, minutes of hypotension ≥75th percentile, year, major procedure, and anesthesia current procedure terminology code body location.

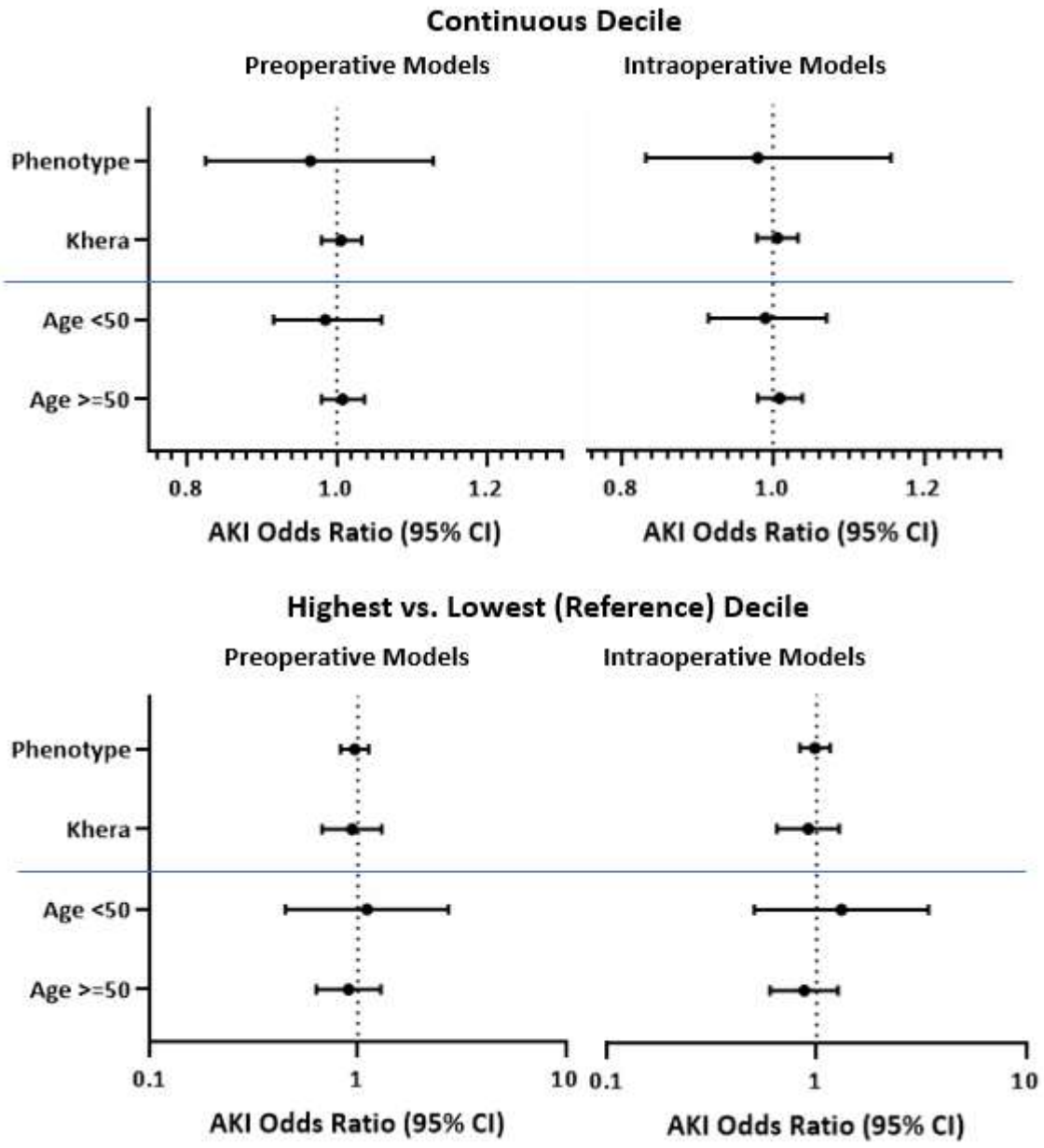


Figure 4.5. Forest plots of adjusted odd of acute kidney injury (AKI) for models containing body mass index polygenic risk scores. Preoperative models were adjusted for age ≥ 50, sex, ASA status ≥ 3, estimated glomerular filtration rate, hypertension, congestive heart failure, peripheral vascular disease, and type 2 diabetes. Intraoperative models were adjusted for preoperative factors, case duration, general anesthesia, fluid volume, packed red blood cell transfusion, minutes of hypotension ≥75th percentile, year, major procedure, and anesthesia current procedure terminology code body location.

Table 4.1. Demographic characteristics of those meeting inclusion criteria of European ancestry and participating in the Michigan Genomics Initiative by acute kidney injury status

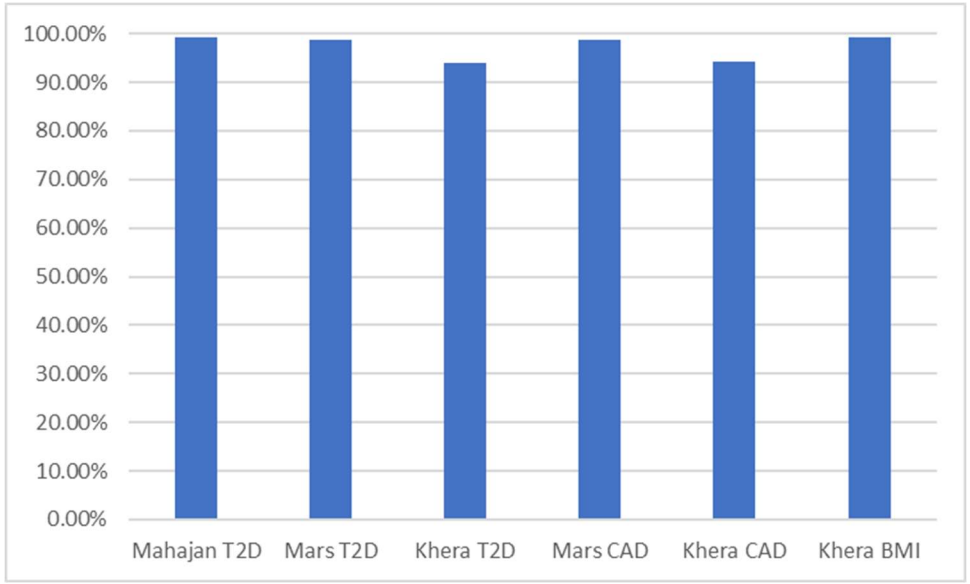
	Overall (N = 14,824)	No Acute Kidney Injury (N = 14,087)	Acute Kidney Injury (N = 737)	P-Value
Demographics				
Age Group (years)				<0.001
18-29	797 (5.4)	767 (5.4)	30 (4.1)	
30-39	1,144 (7.7)	1,117 (7.9)	27 (3.7)	
40-49	1,961 (13.2)	1,886 (13.4)	75 (10.2)	
50-59	3,376 (22.8)	3,205 (22.8)	171 (23.2)	
60-69	4,303 (29.0)	4,063 (28.8)	240 (32.6)	
70-79	2,583 (17.4)	2,418 (17.2)	165 (22.4)	
80+	660 (4.5)	631 (4.5)	29 (3.9)	
Body Mass Index (kg/m2)	29.4 [25.5 to 34.6]	29.4 [25.5 to 34.5]	30.4 [25.9 to 36.3]	0.002
Female Sex	7,372 (49.7)	7,072 (50.2)	300 (40.7)	<0.001
ASA Class				<0.001
1	228 (1.5)	227 (1.6)	1 (0.1)	
2	5,175 (34.9)	5,055 (35.9)	120 (16.3)	
3	8,754 (59.1)	8,243 (58.5)	511 (69.3)	
4	667 (4.5)	562 (4.0)	105 (14.3)	
Estimated Glomerular Filtration Rate	81.2 [66.9 to 97.4]	81.5 [67.5 to 97.5]	72.0 [50.5 to 96.3]	<0.001
Cardiometabolic Conditions				
Hypertension	10,536 (71.1)	9,919 (70.4)	617 (83.7)	<0.001
High Cholesterol	6,449 (43.5)	6,049 (42.9)	400 (54.3)	<0.001
Peripheral Vascular Disorders	2,131 (14.4)	1,941 (13.8)	190 (25.8)	<0.001
Diabetes	3,273 (22.1)	2,998 (21.3)	275 (37.3)	<0.001
Systemic Inflammatory Disorders	1,147 (7.7)	1,104 (7.8)	43 (5.8)	0.047
Hypothyroidism	2,747 (18.5)	2,601 (18.5)	146 (19.8)	0.359
Cardiac Arrhythmias	4,701 (31.7)	4,380 (31.1)	321 (43.6)	<0.001
Congestive Heart Failure	1,812 (12.2)	1,638 (11.6)	174 (23.6)	<0.001
Coronary Artery Disease	2,507 (16.9)	2,300 (16.3)	207 (28.1)	<0.001
Obesity	7,643 (51.6)	7,232 (51.3)	411 (55.8)	0.019
Intraoperative Characteristics				
Procedure Type by Body Location				<0.001
Head	1,685 (11.4)	1,663 (11.8)	22 (3.0)	
Neck	1,095 (7.4)	1,053 (7.5)	42 (5.7)	
Thorax – Extrathoracic	589 (4.0)	567 (4.0)	22 (3.0)	
Thorax – Intrathoracic	1,546 (10.4)	1,468 (10.4)	78 (10.6)	
Spine and Spinal Cord	1,518 (10.2)	1,489 (10.6)	29 (3.9)	
Upper Abdomen	3,362 (22.7)	3,065 (21.8)	297 (40.3)	
Lower Abdomen	1,196 (8.1)	1,081 (7.7)	115 (15.6)	
Gynecologic	220 (1.5)	208 (1.5)	12 (1.6)	
Male Reproductive System	108 (0.7)	106 (0.8)	2 (0.3)	
Pelvis	59 (0.4)	54 (0.4)	5 (0.7)	
Hip/Leg/Foot	2,064 (13.9)	2,015 (14.3)	49 (6.7)	
Shoulder/Arm/Hand	430 (2.9)	420 (3.0)	10 (1.4)	
Radiologic	914 (6.2)	861 (6.1)	53 (7.2)	
Burn	37 (0.3)	36 (0.3)	1 (0.1)	
Other	1 (0.0)	1 (0.0)	0 (0.0)	
Major Procedure (ASA Base Unit >5)	11,299 (76.2)	10,720 (76.1)	579 (78.6)	0.126
Anesthetic Type				
General Anesthesia	12,140 (81.9)	11,485 (81.5)	655 (88.9)	<0.001
Neuraxial	2,379 (16.1)	2,230 (15.8)	149 (20.2)	0.002
Case Duration	217.0 [155.0 to 322.0]	215.0 [154.0 to 317.0]	285.5 [166.0 to 418.0]	<0.001
Packed Red Blood Cell Transfusion	446 (3.0)	375 (2.7)	71 (9.6)	<0.001

Total Fluid Volume, Crystalloid Equivalents (per 500mL)	3.0 [2.0 to 4.6]	3.0 [2.0 to 4.6]	4.0 [2.0 to 7.4]	<0.001
Minutes of MAP <65	9.0 [0.0 to 27.0]	9.0 [0.0 to 26.0]	15.0 [3.0 to 38.0]	<0.001
Nephrotoxic Medication Use	10,607 (71.6)	10,079 (71.6)	528 (71.6)	0.956
Diuretic	193 (1.3)	161 (1.1)	32 (4.3)	<0.001
Antibiotic	10,393 (70.1)	9,875 (70.1)	518 (70.3)	0.915
NSAID	1,456 (9.8)	1,431 (10.2)	25 (3.4)	<0.001

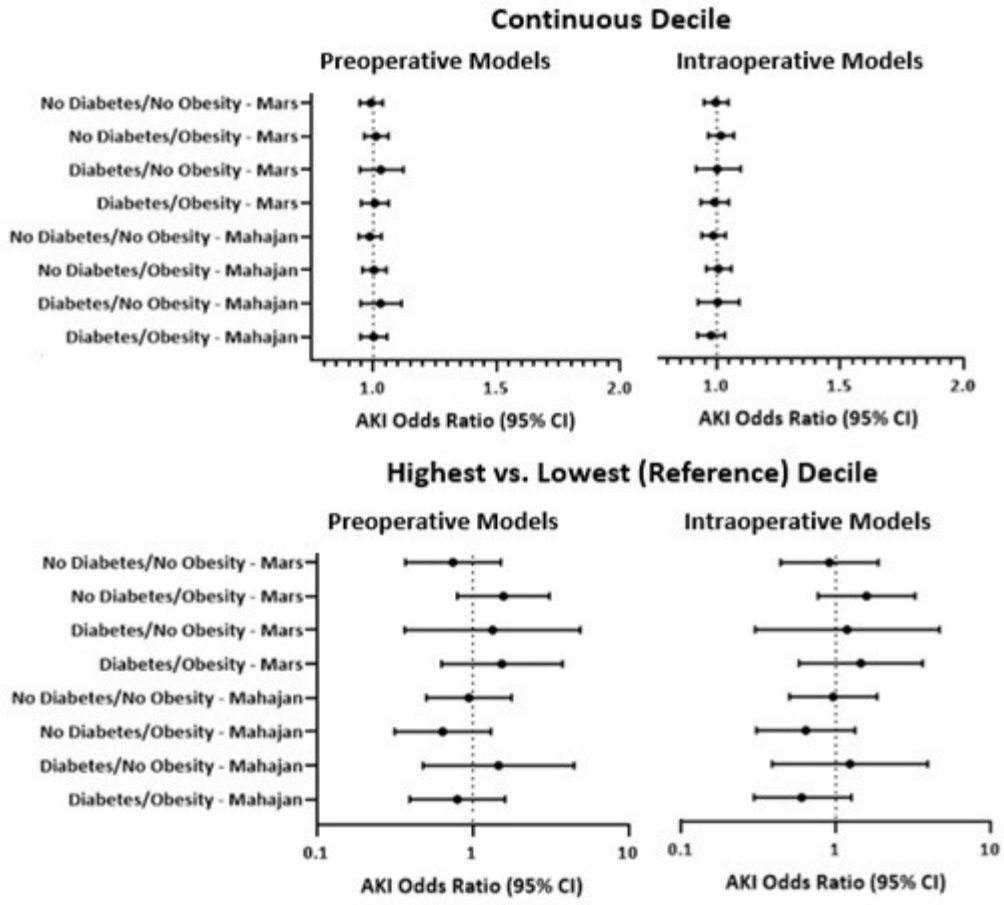
Data are presented as means ± standard deviations, medians [25th percentile to 75th percentile], or frequency (percentage) as appropriate. Anesthetic type is not mutually exclusive.

Appendix D

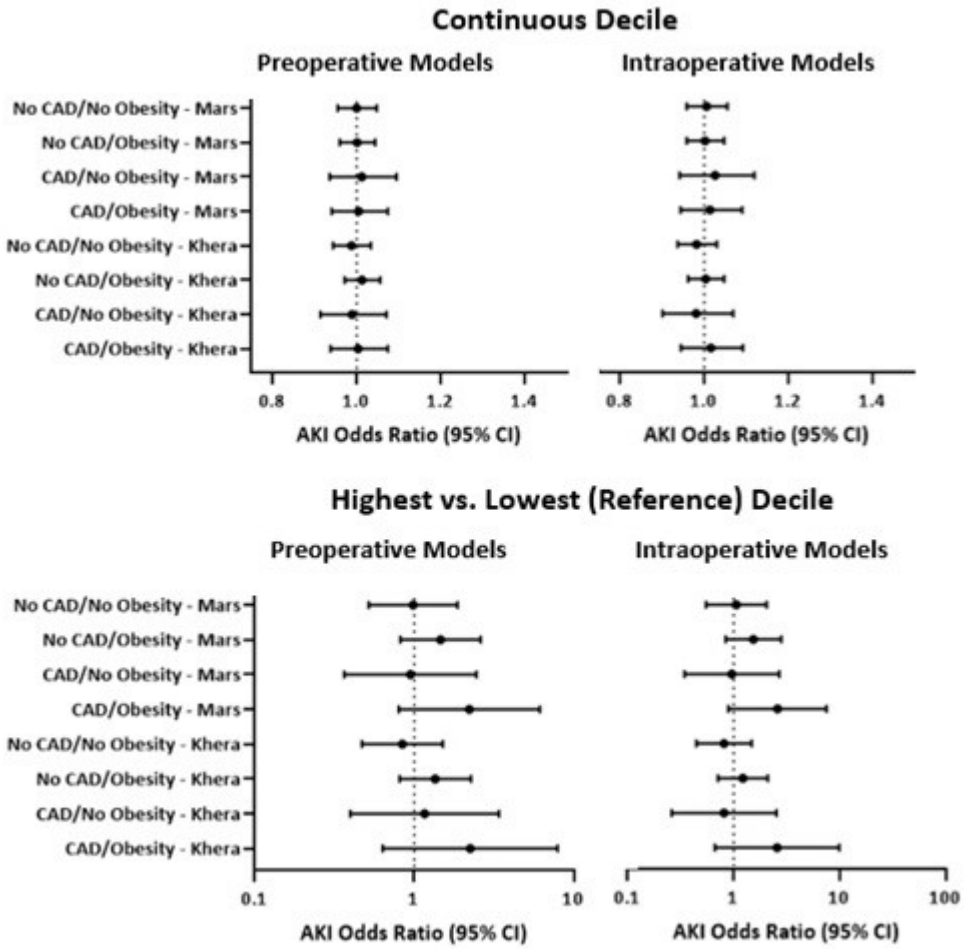
Supplemental Material



Appendix Figure D.1. Percentage of variants included in final score weights. Missing variants were excluded due to imputation quality (Mahajan and Mars), and for both imputation quality and difference in sequencing array used (Khera).



Appendix Figure D.2. Forest plots of adjusted odd of acute kidney injury (AKI) for models containing type 2 diabetes polygenic risk scores stratified by phenotypic diabetes and obesity status. Preoperative models were adjusted for age ≥ 50, sex, ASA status ≥ 3, estimated glomerular filtration rate, hypertension, congestive heart failure, peripheral vascular disease. Intraoperative models were adjusted for preoperative factors, case duration, general anesthesia, fluid volume, packed red blood cell transfusion, minutes of hypotension ≥75th percentile, year, major procedure, and anesthesia current procedure terminology code body location.



Appendix Figure D.3. Forest plots of adjusted odd of acute kidney injury (AKI) for models containing coronary artery disease polygenic risk scores stratified by phenotypic coronary artery disease and obesity status. Preoperative models were adjusted for age ≥ 50, sex, ASA status ≥ 3, estimated glomerular filtration rate, hypertension, congestive heart failure, peripheral vascular disease, and type 2 diabetes. Intraoperative models were adjusted for preoperative factors, case duration, general anesthesia, fluid volume, packed red blood cell transfusion, minutes of hypotension ≥75th percentile, year, major procedure, and anesthesia current procedure terminology code body location.

Appendix Table D.1. List of excluded anesthesia current procedure terminology codes

	Current Procedure Terminology (CPT) Codes
Cardiac	00550, 00560, 00561, 00562, 00563, 00566, 00567, 00580
Renal	00862, 00868
Urologic	00864, 00870, 00872, 00873, 00865, 00908, 00910, 00912, 00914, 00916, 00918, 00860
Labor and Delivery	01958, 01960, 01961, 01968, 01967, 01962, 01969, 01964, 01965, 01966

Appendix Table D.2. Cohort and development information for chosen polygenic risk score weighting files

Study	Journal	GWAS Size	Derivation Cohort	Derivation Cohort Size	Derivation Cohort Ancestry	Method Used	# Variants	Build	PGS#
Type 2 Diabetes									
Khera, 2018	Nat Genet	26,676 cases; 132,532 controls	UKB	120,280 (2,785 cases)	European	LDPred (ρ = 0.01; LD panel = 503 1000G Europeans)	6,917,436	Hg19	PGS000014
Mars, 2020	Nat Med	74,124 cases, 824,006 controls	FINRISK	21,813 (1,346 incident cases, 671 prevalent cases)	European	LDPred (ρ = 0.3; LD radius = 4000; LD reference panel = 2,690 Finnish individuals [autosomal variants only])	6,437,380	Hg19	PGS000330
Mahajan, 2018	Nat Genet	55,005 cases, 400,308 controls	UKB	117,946 (5,639 cases)	European	Pruning and thresholding (P < 0.1; r2 < 0.6)	171,249	GRCh37	PGS000036
Coronary Artery Disease									
Khera, 2018	Nat Genet	60,801 cases, 123,504 controls	UKB	120280 (3963 cases)	European	LDPred (ρ = 0.001; LD panel = 503 1000G Europeans)	6,630,150	Hg19	PGS000013
Mars, 2020	Nat Med	31,355 cases, 377,103 controls	FINRISK	21813 (1209 incidence cases, 954 prevalent cases)	European	LDPred (ρ = 0.003; LD radius = 4000; LD reference panel = 2,690 Finnish individuals [autosomal variants only])	6,423,165	Hg19	PGS000329
Body Mass Index									
Khera, 2019	Cell	238,944 individuals	UKB	119,951	100% European	LDPred (ρ = 0.03; LD reference panel = 503 European samples from 1000 Genomes phase 3	2,100,302	Hg19	PGS000027

Appendix Table D.3. Within-cohort validation model results for polygenic risk scores

		Model 1		Model 2a/b		Model 3	
Phenotype		**Odds Ratio (95%CI)**	**C-Statistic**	**Odds Ratio (95%CI)**	**C-Statistic**	**Odds Ratio (95%CI)**	**C-Statistic**
Type 2 Diabetes	Mars	1.82 (1.74, 1.90)	0.662	NA	0.707/0.708	1.91 (1.83, 2.00)	0.757
	Mahajan	1.86 (1.78, 1.94)	0.660	NA	0.707/0.708	1.94 (1.85, 2.03)	0.756
	Khera	1.33 (1.28, 1.39)	0.580	NA	0.707/0.708	1.43 (1.37, 1.50)	0.724
Coronary Artery Disease	Mars	1.24 (1.19, 1.30)	0.560	NA	0.768/0.769	1.36 (1.30, 1.43)	0.778
	Khera	1.33 (1.27, 1.38)	0.578	NA	0.768/0.769	1.41 (1.35, 1.48)	0.780
		Parameter Estimate (95%CI)	**R^2**	**Parameter Estimate (95%CI)**	**R^2**	**Parameter Estimate (95%CI)**	**R^2**
BMI[a]	Khera	1.93 (1.81, 2.05)	0.063	NA	0.011/0.013	2.00 (1.88, 2.12)	0.077

All effect estimates are per a 1 standard deviation increase in polygenic risk score (PRS)

Model 1: Logistic regression model with the outcome of phenotype, exposure of PRS

Model 2a: Logistic regression model with the outcome of phenotype, covariates age at time of case, BMI at time of case (for non-BMI PRS), genetic-inferred sex

Model 2b: Logistic regression model with the outcome of phenotype, covariates age at time of case, BMI at time of case (for non-BMI PRS), genetic-inferred sex, and the top 10 genetic principal components.

Model 3: Logistic regression model with the outcome of phenotype, exposure of PRS, covariates age at time of case, BMI at time of case (for non-BMI PRS), genetic-inferred sex, and the top 10 genetic principal components.

[a] BMI models presented are linear regression. BMI and polygenic risk score had a correlation of 0.25.

Appendix Table D.4. Definitions of cardiometabolic comorbidities

	ICD 9/10 Definition	Laboratory or Physiologic Definition
Hypertension	40[2-5], 40[2-5].%, I1[1,2,3,5].%, 401.%, 401, I10, I10.%	Baseline SBP ≥ 140mmHg or baseline DBP ≥ 90mmHg or baseline MAP >107mmHg
High Cholesterol	272.[0-4], E78.0, E78.[0-4]%, E78.5	Cholesterol ≥ 200mg/dL, or triglyceride ≥ 150mg/dL, or HDL cholesterol ≤ 40mg/dL for men and ≤ 50mg/dL for women, or LDL cholesterol ≥ 100mg/dL
Peripheral Vascular Disorders	093.0%, 437.3%, 443.[1–9]%, 447.1%, V43.4%, 44[0,1], 44[0,1].%, 557.[1,9]%, I77.1%, Z95.[8,9]%, I73.[1,8,9]%, I79.[0,2]%,K55.[1,8,9]%, I7[0,1].%	N/A
Diabetes	250.[4-9]%, E1[0-4].[2–8]%, 250.[0-3]%, E1[0-4].[0,1,9]%	HbA1c level ≥ 6.5%
Systemic Inflammatory Disorders	446, 446.%, 714, 714.%, 719.3%, 701.0%, 72[0,5], 72[0,5].%, 710.[0–4,8,9]%, 711.2%, 728.5%, 728.89, 729.30, M30.%, M31.[0–3]%, M0[5,6,8].%, M12.[0,3]%, L94.[0,1,3]%, M45.%, M46.[1,8,9]%, M3[2-5].%	N/A
Hypothyroidism	24[3,4], 24[3,4].%, 240.9%, 246.[1,8]%, E0[0-3], E0[0-3].%, E89.0%	Thyroid stimulating hormone laboratory level > 4.0 mU/L
Cardiac Arrhythmias	996.0[1,4], 426.[0,7,9]%, 426.1[0,2,3], 427.[0-4,6-9]%, 785.0%, V45.0%, V53.3%, T82.1%, I44[1-3].%, I45.[69]%, I4[7-9], I4[7-9].%, R00.[0,1,8]%, Z45.0%, Z95.0%	N/A
Congestive Heart Failure	425.[4–9]%, 428, 428.%, 404.[0,1,9]3, 40[2,4].[0,1,9]1, 398.91, I43, I43.%, I42.[0,5–9]%, I25.5%, 150, 150.%, I11.0%, I13.[0,2]%, I09.9%, P29.0%	N/A
Coronary Artery Disease	412, 414.2, 414.8, 414.9, V45.81, V45.82, I25.10, I25.110, I25.111, I25.118, I25.119, I25.2, I25.5, I25.6. I25.700, I25.701, I25.708, I25.709, I25.710, I25.711, I25.718, I25.719, I25.720, I25.721, I25.728, I25.729, I25.730, I25.731, I25.738, I25.739, I25.750, I25.751, I25.758, I25.759, I25.760, I25.761, I25.768, I25.769, I25.790, I25.791, I25.798, I25.799, I25.810, I25.811, I25.812, I25.82, I25.83, I25.84, I25.89, I25.9, Z95.1, Z95.5, Z98.61	N/A
Hypotension	I95.[0-3,8,9], I95.8%, 458.[0,1,8,9], 458.2[1,9], 333.0	Baseline SBP < 90mmHg or baseline DBP <60mmHg or baseline MAP < 70mmHg
Obesity	278.0%, E66.%	Body mass index ≥ 30 kg/m^2

Abbreviations: SBP – systolic blood pressure, DBP – diastolic blood pressure, MAP – mean arterial pressure, HDL - high-density lipoprotein, LDL - low-density lipoproteins

Appendix Table D.5. Demographic characteristics of those cases meeting inclusion criteria by Michigan Genomics Initiative participation status

	Overall (N = 91,895)	No MGI Participation (N = 66,204)	MGI Participation (N = 25,691)	Absolute Standardized Differences
Demographics				
Age Group (years)				0.225
18-29	7,420 (8.1)	5,884 (8.9)	1,536 (6.0)	
30-39	7,325 (8.0)	5,356 (8.1)	1,969 (7.7)	
40-49	10,890 (11.9)	7,589 (11.5)	3,301 (12.9)	
50-59	19,143 (20.8)	13,184 (19.9)	5,959 (23.2)	
60-69	24,316 (26.5)	16,958 (25.6)	7,358 (28.6)	
70-79	16,319 (17.8)	11,875 (17.9)	4,444 (17.3)	
80+	6,482 (7.1)	5,358 (8.1)	1,124 (4.4)	
Body Mass Index (kg/m2)	28.5 [24.3 to 33.7]	28.1 [24.0 to 33.3]	29.2 [25.1 to 34.4]	0.130
Female Sex	43,395 (47.2)	30,971 (46.8)	12,424 (48.4)	0.032
ASA Class				0.256
1	1,355 (1.5)	1,052 (1.6)	303 (1.2)	
2	21,668 (23.6)	14,474 (21.9)	7,194 (28.0)	
3	56,772 (61.8)	40,504 (61.2)	16,268 (63.3)	
4	12,100 (13.2)	10,174 (15.4)	1,926 (7.5)	
Cardiometabolic Conditions				
Hypertension	66,788 (72.7)	48,282 (72.9)	18,506 (72.0)	0.020
High Cholesterol	41,345 (45.0)	29,547 (44.6)	11,798 (45.9)	0.026
Peripheral Vascular Disorders	20,496 (22.3)	15,547 (23.5)	4,949 (19.3)	0.103
Diabetes	23,597 (25.7)	17,090 (25.8)	6,507 (25.3)	0.011
Systemic Inflammatory Disorders	7,259 (7.9)	4,991 (7.5)	2,268 (8.8)	0.047
Hypothyroidism	17,471 (19.0)	12,422 (18.8)	5,049 (19.7)	0.023
Cardiac Arrhythmias	40,360 (43.9)	30,626 (46.3)	9,734 (37.9)	0.170
Congestive Heart Failure	18,180 (19.8)	13,924 (21.0)	4,256 (16.6)	0.115
Coronary Artery Disease	19,576 (21.3)	14,606 (22.1)	4,970 (19.4)	0.067
Obesity	42,859 (46.6)	29,528 (44.6)	13,331 (51.9)	0.146
Intraoperative Characteristics				
Procedure Type by Body Location				0.254
Head	7,861 (8.6)	5,310 (8.0)	2,551 (9.9)	
Neck	5,469 (6.0)	3,647 (5.5)	1,822 (7.1)	
Thorax – Extrathoracic	4,475 (4.9)	3,291 (5.0)	1,184 (4.6)	
Thorax – Intrathoracic	11,304 (12.3)	8,438 (12.8)	2,866 (11.2)	
Spine and Spinal Cord	5,570 (6.1)	3,368 (5.1)	2,202 (8.6)	
Upper Abdomen	23,372 (25.4)	17,213 (26.0)	6,159 (24.0)	
Lower Abdomen	6,959 (7.6)	4,988 (7.5)	1,971 (7.7)	
Gynecologic	836 (0.9)	547 (0.8)	289 (1.1)	
Male Reproductive System	439 (0.5)	288 (0.4)	151 (0.6)	
Pelvis	623 (0.7)	489 (0.7)	134 (0.5)	

Hip/Leg/Foot	11,803 (12.8)	8,271 (12.5)	3,532 (13.8)	
Shoulder/Arm/Hand	2,227 (2.4)	1,570 (2.4)	657 (2.6)	
Radiologic	9,629 (10.5)	7,615 (11.5)	2,014 (7.8)	
Burn	1,312 (1.4)	1,154 (1.7)	158 (0.6)	
Other	16 (0.0)	15 (0.0)	1 (0.0)	
Major Procedure (ASA Base Unit >5)	57,959 (63.1)	39,951 (60.4)	18,008 (70.1)	0.206
Anesthetic Type				
General Anesthesia	68,270 (74.3)	47,994 (72.5)	20,276 (78.9)	0.150
Neuraxial	10,023 (10.9)	6,559 (9.9)	3,464 (13.5)	0.112
Case Duration	179.0 [113.0 to 271.0]	171.0 [106.0 to 260.0]	200.0 [135.0 to 300.0]	0.226
Packed Red Blood Cell Transfusion	3,743 (4.1)	2,844 (4.3)	899 (3.5)	0.041
Total Fluid Volume, Crystalloid Equivalents (per 500mL)	2.2 [1.2 to 3.8]	2.0 [1.2 to 3.6]	2.6 [1.6 to 4.2]	0.151
Minutes of MAP <65	6.0 [0.0 to 21.0]	6.0 [0.0 to 21.0]	8.0 [0.0 to 24.0]	0.081
Nephrotoxic Medication Use	50,992 (55.5)	34,503 (52.1)	16,489 (64.2)	0.246
Diuretic	1,199 (1.3)	894 (1.4)	305 (1.2)	0.015
Antibiotic	49,728 (54.1)	33,587 (50.7)	16,141 (62.8)	0.246
NSAID	6,386 (7.0)	4,215 (6.4)	2,171 (8.5)	0.080
Outcome				
Acute kidney injury	6,720 (7.3)	5,162 (7.8)	1,558 (6.1)	0.068

Data are presented as means ± standard deviations, medians [25th percentile to 75th percentile], or frequency (percentage) as appropriate. Data represent cases from 59,724 unique patients. Anesthetic type is not mutually exclusive.

Appendix Table D.6. Model odds ratios with 95% confidence intervals and overall c-statistics for data presented in figures 3-5.

	Continuous Polygenic Risk Score Decile				Highest Decile vs. Lowest Decile (Reference)			
	Preoperative Model		Intraoperative Model		Preoperative Model		Intraoperative Model	
Model	**Adjusted OR (95%CI)**	**Model C-Statistic**	**Adjusted OR (95%CI)**	**Model C-Statistic**	**Adjusted OR (95%CI)**	**Model C-Statistic**	**Adjusted OR (95%CI)**	**Model C-Statistic**
Type 2 Diabetes								
Phenotype	1.55 (1.31, 1.82)	0.674	1.52 (1.28, 1.80)	0.785	1.55 (1.31, 1.82)	0.674	1.52 (1.28, 1.80)	0.785
Mars PRS	1.02 (0.99, 1.05)	0.666	1.02 (0.99, 1.05)	0.781	1.46 (1.04, 2.06)	0.666	1.43 (1.00, 2.05)	0.781
Mahajan PRS	1.02 (0.99, 1.05)	0.665	1.01 (0.99, 1.04)	0.780	1.14 (0.83, 1.56)	0.666	1.04 (0.75, 1.44)	0.781
No Diabetes/No Obesity – Mars	0.99 (0.95, 1.04)	0.676	0.99 (0.95, 1.05)	0.812	0.75 (0.37, 1.52)	0.677	0.91 (0.44, 1.88)	0.812
No Diabetes/Obesity – Mars	1.01 (0.96, 1.06)	0.650	1.02 (0.97, 1.07)	0.795	1.57 (0.80, 3.11)	0.654	1.58 (0.77, 3.25)	0.795
Diabetes/No Obesity – Mars	1.03 (0.95, 1.12)	0.652	1.00 (0.92, 1.10)	0.756	1.34 (0.37, 4.90)	0.655	1.18 (0.30, 4.66)	0.757
Diabetes/Obesity - Mars	1.01 (0.95, 1.06)	0.645	0.99 (0.94, 1.05)	0.760	1.54 (0.63, 3.76)	0.645	1.45 (0.58, 3.63)	0.760
No Diabetes/No Obesity – Mahajan	0.99 (0.94, 1.03)	0.677	0.99 (0.94, 1.04)	0.812	0.95 (0.51, 1.78)	0.677	0.96 (0.50, 1.84)	0.813
No Diabetes/Obesity – Mahajan	1.00 (0.96, 1.05)	0.650	1.01 (0.96, 1.06)	0.794	0.64 (0.62, 1.31)	0.654	0.64 (0.31, 1.33)	0.795
Diabetes/No Obesity – Mahajan	1.03 (0.95, 1.12)	0.649	1.00 (0.92, 1.09)	0.756	1.47 (0.48, 4.47)	0.658	1.23 (0.39, 3.92)	0.757
Diabetes/Obesity - Mahajan	1.00 (0.95, 1.06)	0.645	0.98 (0.92, 1.03)	0.760	0.80 (0.40, 1.62)	0.651	0.60 (0.29, 1.26)	0.761
Age < 50 – Mars	1.02 (0.95, 1.10)	0.766	1.01 (0.93, 1.10)	0.849	1.81 (0.58, 5.63)	0.769	1.35 (0.41, 4.42)	0.849
Age ≥ 50 – Mars	1.02 (0.99, 1.05)	0.647	1.02 (0.99, 1.05)	0.777	1.41 (0.98, 2.04)	0.647	1.42 (0.97, 2.09)	0.777
Age < 50 – Mahajan	0.96 (0.90, 1.03)	0.767	0.95 (0.88, 1.02)	0.847	0.45 (0.17, 1.16)	0.766	0.46 (0.17, 1.26)	0.846
Age ≥ 50 - Mahajan	1.03 (0.99, 1.06)	0.645	1.02 (0.99, 1.05)	0.777	1.28 (0.91, 1.80)	0.649	1.19 (0.84, 1.69)	0.778
Coronary Artery Disease								
Phenotype	1.03 (0.85, 1.25)	0.674	1.08 (0.88, 1.32)	0.785	1.03 (0.85, 1.25)	0.674	1.08 (0.88, 1.32)	0.785
Mars PRS	1.00 (0.98, 1.03)	0.674	1.01 (0.98, 1.04)	0.785	1.33 (0.93, 1.89)	0.675	1.42 (0.99, 2.03)	0.785
Khera PRS	0.99 (0.97, 1.03)	0.674	0.99 (0.97, 1.02)	0.785	1.11 (0.80, 1.55)	0.674	1.02 (0.73, 1.44)	0.785
No CAD/No Obesity – Mars	1.00 (0.96, 1.05)	0.681	1.01 (0.96, 1.06)	0.816	0.984 (0.52, 1.87)	0.685	1.06 (0.55, 2.05)	0.817
No CAD/Obesity – Mars	1.00 (0.96, 1.04)	0.650	1.00 (0.96, 1.05)	0.786	1.46 (0.82, 2.61)	0.653	1.54 (0.84, 2.81)	0.787
CAD/No Obesity – Mars	1.01 (0.94, 1.10)	0.676	1.03 (0.94, 1.12)	0.786	0.95 (0.36, 2.46)	0.679	0.96 (0.34, 2.69)	0.791
CAD/Obesity - Mars	1.01 (0.94, 1.07)	0.660	1.01 (0.94, 1.09)	0.796	2.21 (0.80, 6.14)	0.664	2.60 (0.89, 7.53)	0.798
No CAD/No Obesity – Khera	0.99 (0.94, 1.03)	0.682	0.98 (0.94, 1.03)	0.816	0.84 (0.47, 1.51)	0.682	0.81 (0.45, 1.48)	0.816
No CAD/Obesity – Khera	1.01 (0.97, 1.06)	0.650	1.00 (0.96, 1.05)	0.786	1.35 (0.81, 2.27)	0.650	1.22 (0.71, 2.10)	0.786
CAD/No Obesity – Khera	0.99 (0.91, 1.07)	0.675	0.98 (0.90, 1.07)	0.787	1.16 (0.40, 3.40)	0.678	0.81 (0.26, 2.54)	0.786
CAD/Obesity - Khera	1.00 (0.94, 1.07)	0.660	1.02 (0.95, 1.09)	0.796	2.24 (0.64, 7.94)	0.672	2.58 (0.67, 9.95)	0.801
Age < 50 – Mars	0.95 (0.88, 1.03)	0.766	0.95 (0.87, 1.03)	0.849	1.14 (0.34, 3.86)	0.772	1.04 (0.30, 3.68)	0.850
Age ≥ 50 – Mars	1.01 (0.98, 1.04)	0.658	1.02 (0.99, 1.05)	0.784	1.37 (0.95, 1.98)	0.659	1.52 (1.04, 2.22)	0.784
Age < 50 – Khera	0.98 (0.91, 1.05)	0.765	0.96 (0.89, 1.04)	0.848	0.82 (0.31, 2.14)	0.766	0.64 (0.23, 1.84)	0.849
Age ≥ 50 - Khera	1.00 (0.98, 1.03)	0.659	1.00 (0.97, 1.03)	0.784	1.18 (0.83, 1.68)	0.659	1.11 (0.77, 1.60)	0.784
Body Mass Index								
Phenotype	0.97 (0.83, 1.13)	0.674	0.98 (0.83, 1.16)	0.785	0.97 (0.83, 1.13)	0.674	0.98 (0.83, 1.16)	0.785
Khera PRS	1.01 (0.98, 1.03)	0.674	1.01 (0.98, 1.03)	0.785	0.94 (0.67, 1.30)	0.674	0.91 (0.65, 1.28)	0.785
Age < 50 – Khera	0.99 (0.92, 1.06)	0.764	0.99 (0.92, 1.07)	0.848	1.11 (0.45, 2.73)	0.767	1.31 (0.50, 3.42)	0.849
Age ≥ 50 - Khera	1.01 (0.98, 1.04)	0.659	1.01 (0.98, 1.04)	0.784	0.90 (0.63, 1.29)	0.659	0.87 (0.60, 1.26)	0.784

Preoperative models were additionally adjusted for age ≥ 50, sex, ASA status ≥ 3, estimated glomerular filtration rate, hypertension, congestive heart failure, peripheral vascular disease, and type 2 diabetes phenotype (coronary artery disease and body mass index PRS models). Intraoperative models were adjusted for preoperative factors, case duration, general anesthesia, fluid volume, packed red blood cell transfusion, minutes of hypotension ≥75th percentile, year, major procedure, and anesthesia current procedure terminology code body location.

Chapter 5

Conclusions

5.1 Summary of Findings

This dissertation examines the associations between obesity with and without comorbid cardiometabolic disease and postoperative acute kidney injury in both a multicenter cohort of total knee and hip replacement procedures, and a single-center non-cardiac, non-renal, non-urologic, non-liver transplant procedure cohort enhanced with genetic data.

In Chapter 2 (Aim 1), we evaluated latent classes of cardiometabolic conditions among patients in the multicenter cohort of total joint arthroplasty cases and found three robust groups: (1) a class with moderate probability of hypertension and low probability of other factors representing 45.2% (n = 37,032) of the population; (2) a class with high probability of hypertension and high cholesterol and moderate probability of diabetes representing 45.1% (n=36,889) of the population; and (3) a class with high probability of hypertension, high cholesterol, cardiac arrhythmias, coronary artery disease (CAD), and congestive heart failure (CHF), and moderate probability of diabetes and peripheral vascular disease representing 9.7% (n=7,950) of the population. Obesity and cardiovascular disease were associated with increased risk of AKI within 7 days following surgery. Compared to those in class (1) without obesity, those in class (3) with obesity had 3.6 times the odds of AKI (95%CI:3.1,4.3) while those in class (3) without obesity had 2.5 times the odds of AKI (95%CI:2.0,3.0) compared to the same group. Individuals with more significant cardiometabolic disease had higher odds of AKI regardless of the presence of obesity, though obesity showed additional risk.

In Chapter 3 (Aim 2), we used the same multicenter cohort to examine hypothesized mediation by modifiable intraoperative factors including general anesthesia use and minutes of intraoperative hypotension. We found little evidence of a clinically or statistically significant mediating effect of general anesthesia use or minutes of hypotension on the relationship between preoperative cardiometabolic comorbidity latent class and acute kidney injury. This suggests that while these perioperative factors are independent risk factors for acute kidney injury, controlling them intraoperatively does not meaningfully reduce the risk of AKI conferred by cardiometabolic comorbidity.

In Chapter 4 (Aim 3), we utilized validated and published polygenic risk scores (PRS) for type 2 diabetes, coronary artery disease, and BMI in a single-center cohort of surgical patients to assess the association between these PRS and postoperative AKI. There was little evidence of an association between PRS and AKI both overall and after adjustment. Notably, however, we found that the PRS performed similarly to the disease phenotype when assessing overall model discrimination, indicating the potential utility of these scores in datasets where robust electronic health record data for these complex conditions are not available, or where the phenotype may not yet have occurred.

Overall, the results of the three aims add to the current literature regarding risks of postoperative AKI. The latent classes produced in Aim 1 quantified risks of AKI that are substantially higher than those published for individual cardiometabolic comorbidities[8,14]. This work highlights the methodological utility of latent class analysis to determine clinically meaningful groups of individuals at higher risk of AKI; such a method goes beyond the *a priori* fixed cardiometabolic group definition as employed by Glance et al[13]. While mediation analysis has not been broadly used within the anesthesia literature, it can provide much-needed insight

into the underlying mechanisms for AKI and other postoperative conditions. Though we did not observe clinically significant mediation, similar analyses of full renal-sparing protocols may prove more informative. Finally, the use of polygenic risk scores of related cardiometabolic conditions was a novel application of this methodology within the AKI literature.

5.2. Public Health Implications

The treatment of obesity and associated conditions such as type 2 diabetes and hypertension have largely focused on weight loss, ignoring physiological and psychosocial barriers to achieving a sustained decrease in weight[31]. In 2020, the Canadian Medical Association released radical clinical guidelines for the treatment of obesity[31]. They focus on patient-centered goals around reducing risk of developing comorbid conditions such as diabetes, and recognize that BMI is only one measurement of an individual's health, and an ideal BMI may not be an individual's best weight. Additionally, they recognize that the built environment, including cultural, socioeconomic, and social factors affect an individual's ability to follow a lifestyle that results in a significant reduction in weight. Importantly, the guidelines highlight the importance of concurrently treating mental health conditions such as depression, which may be contributing to an individual's higher weight[31]. These guidelines are only the first step in a critically needed reframing of the conversation around obesity, diabetes, and other cardiometabolic diseases in today's clinical and community settings.

The Canadian Medical Association guidelines are particularly relevant within the total joint arthroplasty population, where many institutions and surgeons implement a strict BMI cutoff for those who receive this quality-of-life procedure. Obesity is a known risk factor for osteoarthritis, and that risk increases with the presence of additional cardiometabolic diseases such as diabetes[34], and osteoarthritis is a common indication for elective knee and hip

replacement procedures, which may be performed over 5 years earlier in obese patients than those of normal weight[35,36]. As shown in both the new guidelines and previous literature, increasing physical activity has been shown to improve cardiovascular fitness and reduce the risk of conditions such as type 2 diabetes and hypertension even in obese individuals[32,33]. Increased activity has also been shown to significantly improve HbA1c values and increase insulin sensitivity within diabetic individuals[149,150]; such glucose control is vital to the successful management of diabetes and reduction of risk of diabetic complications.

For obese individuals experiencing significant osteoporotic pain with movement, total joint arthroplasty is imperative to facilitating more movement, and thus reducing risk of developing additional comorbidity. Although research has been mixed on whether functional gains following these procedures are comparable between obese and non-obese individuals[110,111], comparable decreases in pain and improvements of quality of life are well-established[110,151]. Arthroplasty can therefore prove to be a significant intervention point in the prevention of obesity-related sequelae such as type 2 diabetes, or in facilitating successful diabetic management for those who already have the condition. However, questions still remain on whom it is safe to perform these procedures on, and whether the TJA should be performed in an outpatient or inpatient setting.

Indeed, the differential risk stratification for AKI by cardiometabolic latent class and exacerbated by obesity observed in Aim 1 of this dissertation support the argument that an individual's complete risk profile should be assessed when making the decision to operate, rather than a singular condition. While we have only examined the outcome of AKI in this dissertation, literature examining the risk of postoperative complications such as infection rarely account for patterning of conditions such as diabetes with obesity. This dissertation contributes to a better

understanding of how different presentations of cardiometabolic disease and obesity may influence the observed risk associations for postoperative outcomes.

Conversations regarding risks and benefits of receiving a given procedure are especially relevant given more surgeries are being performed in an outpatient setting. Those at increased risk for complications such as AKI, which can in most cases only be diagnosed with a blood draw, may benefit from increased monitoring in the week following surgery; additional blood draws are not routinely performed after the patient leaves the hospital. The findings from Aim 1 show that we can predict those a high risk for AKI based on patterning of cardiometabolic disease. Then, in Aim 2, we observed minimal mediation of the effect of cardiometabolic latent class on AKI risk by modifiable intraoperative factors. This suggests that use of certain renal-sparing intraoperative protocols do not attenuate the significant risk conferred by having certain combinations of these cardiometabolic conditions. This dissertation expands upon current research examining associations between intraoperative procedures and AKI, specifically showing that in our cohort it is not possible to mitigate the mechanical damage of these conditions by changing intraoperative factors. Together, these results suggest that those with multiple cardiometabolic conditions may benefit from additional postoperative monitoring such as an additional laboratory work to assess creatinine values, especially if they procedure was performed in the outpatient setting. Such assessments could be easily performed at the postoperative follow-up visit within the clinic, or by a phlebotomy-trained community healthcare worker.

As a whole, the results of this dissertation have implications well beyond the surgical cohorts studied. Acute kidney injury can occur in over 30% of cardiac procedures, in addition to high rates in the critical care population[152]. Risk stratification to prioritize early testing for

detection of AKI and other postoperative outcomes such as surgical site infection or myocardial infarction is imperative to reducing the likelihood of adverse downstream sequelae. The examination of clusters of cardiometabolic comorbidity provide novel insight into groups of individuals potentially at higher risk for such conditions; it is likely that differential comorbid presentation of cardiometabolic diseases would be seen across surgical and critical care cohorts. While we could not discern temporality of individual condition diagnoses within an individual, further examination of cardiometabolic disease patterning may help elucidate the underlying etiology of a number of postoperative outcomes.

The results of this dissertation suggest that the risk conferred by comorbid presentation of these conditions is greater than the individual risks previously reported in the literature[8,14]. Given that these conditions often do not occur in isolation, comorbid presentation should be considered in the creation of risk-stratification models for postoperative outcomes such as AKI, myocardial infarction, stroke, and others. There has been a more recent trend towards incorporating such risk prediction models within the electronic health record system, and incorporating alerts to physicians when a certain threshold for risk has been reached. These models could be coded into the electronic health record system for postoperative outcomes incorporating data from pre-operative risks such as age, sex, and comorbid cardiometabolic disease presentation, with the risk for the given outcome being updated as intraoperative events occur, such as blood transfusions or use of cardiopulmonary bypass. If a higher risk level is indicated preoperatively or develops following events within the intraoperative setting, notification could then help inform clinicians on whether additional post-operative monitoring or screening may be warranted for individuals determined to be at significantly increased risk.

There is precedent for such a real-time prediction modeling within the Michigan Medicine EHR system for healthcare-associated *Clostridioides difficile* infection[100]. Briefly, risk-prediction models for development of the infection were constructed using multitask regularized logistic regression and included both time-varying information such as laboratory data, vital signs, and time-invariant patient demographics; a patient's risk level for each day of the hospital stay was predicted. The model construction was based on previously validated work for retrospective prediction of *Clostridioides difficile* infection[153]. Notably, though there was a minor decrease in model performance between retrospective (area under the receiver operating characteristic curve (AUROC) 0.778) and prospective validation cohorts (AUROC 0.767), this was determined to be due to the difference in underlying pipeline infrastructure between real-time and retrospective data availability rather than changes in clinical practice or patient population over time. If such retrospectively derived and prospectively utilized risk prediction models are to be integrated within the EHR, it is vital that these models be examined for such differences with prospectively collected data at regular intervals to ensure accurate performance. Within the postoperative setting, major changes in standard surgical procedures in particular may change the predictability of such models. Overall, the structure presented by Wiens[153] and Otles[100] could serve as a foundation for developing a similar model for prediction of postoperative outcomes to better facilitate early detection and treatment, and to hopefully improve patient outcomes.

This dissertation has highlighted the multifactorial nature and utility of the electronic health record for epidemiological research, in addition to clinical applications. The EHR provides a unique resource of often longitudinal data of an individual's progression through the life-course, including the development and advancement of diseases. There is increasing interest

in the utility of EHR data not only for individuals but for populations over time. With the increasing cost of prospective research, the gold standard for epidemiological and other studies, there is interest in leveraging existing resources to simulate such studies at reduced cost. This dissertation showed the use of a robust clinical EHR, optimized for research use through the Research Data Warehouse and MPOG databases, to answer both clinical and epidemiological questions. Specifically, the EHR was used to retrospectively identify common cardiometabolic diseases which predict risk of an incident outcome. It is easy to imagine varied applications of this rich data resource, such as to evaluate the effects of institutional change in standard of care for treatment of a patient newly presenting with type 2 diabetes on glucose control with medication and diet recommendations as measured by longitudinal change in hemoglobin A1c values. These large cohorts of individuals can and should be leveraged for all facets of public health.

The third aim of this dissertation used polygenic risk scores for type 2 diabetes, coronary artery disease, and body mass index within an electronic health record database containing a robust, well-defined phenotype. In such a scenario, PRS should not be used in lieu of the phenotype itself; rather, the strength in including PRS here lies in the ability to further differentiate environmental risk from genetic risk. This distinction is important when determining what direction to steer research initiatives and development of intervention strategies. However, there are a number of potential research use-cases for PRS in which the phenotype may not be as well-defined.

First, the phenotype may be poorly defined due to difficulties in measurement. Ovarian and pancreatic cancers, for example, do not have screening tests available, and given the location of the affected organs and non-specific symptomology are often not diagnosed until much later

in the disease course[154,155]. In such instances it may not be feasible within the confines of a research study to perform diagnostic imaging or other testing on all participants to determine their true phenotype for the condition. Polygenic risk scores could therefore be used here in lieu of the phenotype of interest (i.e. high genetic risk, moderate genetic risk, low genetic risk) or in conjunction with the phenotype (i.e. no recorded pancreatic cancer phenotype but high genetic risk for pancreatic cancer) when the phenotype is a confounder, effect modifier, or mediator of interest within statistical modeling.

Second, there are many genetic cohorts not linked to electronic health record or self-reported disease status, resulting in missing phenotypes. This is particularly of concern when the missing phenotype is significantly associated with the outcome of interest; for example, type 2 diabetes phenotype in a study of cardiovascular-related mortality. In such cases, PRS for the phenotype could be used in lieu of the phenotype, potentially dichotomized as high genetic risk for the phenotype versus low genetic risk for the phenotype, to more accurately construct risk prediction models for the outcome of interest. In this instance, the use of published, well-constructed, and validated PRS within a similar ancestry population is critical as there is no phenotype to assess validity within the study cohort.

Lastly, there may be instances where the phenotype has not yet happened, such as a cohort of younger individuals when a phenotype of interest is more commonly found in older adults (e.g. Alzheimer's disease). Polygenic risk scores may be best utilized in these instances in conjunction with biomarkers for subclinical disease as a measure of potential to develop the condition; such risk determination could be used to guide research on populations that could benefit from early interventions. Additionally, such a cohort provides an opportunity to study the

associations of genetic risk (via PRS) and environmental interaction on early-onset presentation of these phenotypes.

5.3 Strengths and Limitations

This dissertation has several strengths. First, the large sample size of over 80,000 joint arthroplasty patients for Aims 1 and 2, and 14,000 for Aim 3 allowed for a robust cohort of those with both the cardiometabolic conditions of interest and those with the rare outcome of acute kidney injury. Second, a major strength of Aims 1 and 2 lies in the multicenter nature of the dataset, which allows for the examination of a relatively rare condition following outpatient joint replacement surgery. Differences in institutional practice and populations increase the generalizability of the findings. Third, the large European ancestry population within the MGI dataset used in Aim 3 allowed for a wider selection of potential published polygenic risk scores for use within our analytic cohort; a vast majority of published PRS for these conditions have been derived and validated in those of European ancestry. Fourth, across all aims innovative methodology such as the use of latent classes and PRS for cardiometabolic disease were used to consider the effect of cardiometabolic conditions on risk of AKI.

This dissertation does have some potential limitations. First, institutional practice patterns may limit those who get certain non-urgent elective surgeries, especially joint replacement, to healthier populations, making it more difficult to accurately assess associations between comorbidities and the outcome. This practice introduces selection bias at the hospital level, and as a result downstream selection bias into the resulting analytic cohort, with differential likelihood of being in the analytic cohort changing based on healthcare system. For a single center study, this bias could significantly attenuate the results as more individuals who developed AKI in the sample would be healthier, an effect compounded by small sample size of the

outcome. Results from such studies may not be generalizable to institutions with broader inclusion criteria for these surgeries. However, within our sample this selection bias is less of a concern given 30 institutions were included, accounting for a variety of arthroplasty surgical inclusion criteria and a range of rates of AKI. Future work should be conducted to assess the influence of selection bias at the hospital level on the results from studies such as this.

Second, due to the retrospective nature of the data, there may be under-reporting or mis-reporting of some of the cardiometabolic conditions and AKI. This is a common limitation of electronic health record data, where the recorded information was collected for clinical care rather than for research purposes. Further, the accuracy and completeness of the data may vary by institutional practice, electronic health record structure, interoperability between healthcare systems, and physician decision-making. To minimize the inherent potential for misclassification biases, a multi-factorial definition of cardiometabolic comorbidities was implemented. Third, the findings of this study may not be generalizable to other surgical cohorts, particularly those where the surgery type significantly increases risk of AKI such as cardiovascular procedures. The purpose of this study was to examine the associations between cardiometabolic disease clustering and AKI. As such clustering has not before been examined in relation to AKI, the analytic cohort was designed to reduce intraoperative heterogeneity by examining a single elective surgical procedure. Future extensions of this work in cohorts such as cardiac surgery should therefore examine the mediation effects of surgical procedure or use of cardiopulmonary bypass in addition to the direct effect of cardiometabolic cluster on AKI.

Finally, the potential for unmeasured confounding is always a concern for epidemiological research, particularly for mediation analyses where no unmeasured confounding of the relationships is an assumption which must hold for causal inference to be made. One way

to measure the strength of an unmeasured confounder needed to nullify the results seen is the e-value. While every effort was made to make to include all potential confounders in our analysis, this is not realistically feasible; our analysis did include confounders which based on literature review had known large associations with development of postoperative AKI such as intraoperative blood transfusion. While other risk factors for AKI such as preoperative anemia were not included in the analysis, they are unlikely to be confounders of the exposure-mediator, exposure-outcome, or mediator-outcome pathways. If an unmeasured confounder did exist, it would need to have a very strong effect to nullify the observed results based on our computed e-value of 6.12 for the results in Aim 2.

5.4 Future Research Directions

This dissertation provides new information on how patterning of cardiometabolic comorbidities and obesity affects risk of acute kidney injury following total knee and hip arthroplasty, as well as how use of polygenic risk scores for these conditions can be used in prediction models for the same outcome in a more generalized surgical cohort. Several directions can be taken in future research to further explore the findings presented above.

First, while the cross-sectional nature of the current study cannot assess temporality within cardiometabolic conditions and obesity, the increased risk for AKI of those with greater comorbidity is suggestive of the effects of a prolonged or poorly treated disease course. For example, it has been hypothesized that the increased risk of AKI for those who are diabetic is related to vascular damage from a hyperglycemic and inflammatory state, and in more severe cases of diabetes may also be related to atherosclerosis changes within the kidney which would reduce functionality[88]. Future studies could examine the duration and effectiveness of treatment for these conditions, and how glucose control affects the risk of AKI; for example, trajectories of

HbA1c values in the two years preceding the surgical procedure could be examined to assess if different patterns of glucose control differentially increased risk of AKI. A similar study could be conducted prospectively examining variability in glucose as measured by wearable continuous-tracking glucose monitors.

Likewise, the results of Aim 2 suggest that utilizing renal-sparing techniques do not meaningfully mitigate the risk already conferred by preoperative cardiometabolic disease. Future work is needed to more fully elucidate the processes by which the cardiometabolic diseases contribute to postoperative AKI risk, with a focus on the complex interplay between the potential inflammatory effects of obesity and comorbid cardiometabolic conditions. Specifically, future studies should examine the association of inflammation (via serum levels of c-reactive protein, interleukin-6, or other proinflammatory cytokines) within those who are metabolically healthy obese and those who are metabolically unhealthy obese with development of postoperative outcomes such as AKI to determine the extent of deleterious systemic effects of this condition. Additionally, more research into the effectiveness of renal-sparing techniques in the prevention of AKI is warranted.

Third, given the limitations of the dataset used for Aim 3, we did not have the sample size to fully examine the utility of these scores in subpopulations of individuals such as those with diabetes but without obesity. We additionally were unable to study the use of these scores in those of non-European majority ancestry. Additional research is needed into whether the effect of PRS seen in the current study is consistent for those of non-European ancestry when the cardiometabolic PRS for those of other ancestry groups are constructed from large ancestry-specific GWAS. Future work could also examine the associations of additional PRS of interest, such as scores for inflammation or glucose metabolism, physiologic processes which, when

dysregulated, may result in disease. Higher levels of inflammation due to a hyperglycemic state are thought to potentially mediate the pathway between type 2 diabetes and development of AKI. Therefore, high genetic risk for these conditions may provide additional insight into risk of developing AKI postoperatively.

Finally, AKI is only one of many potential adverse postoperative events. Similar studies should be conducted for other outcomes associated with cardiometabolic disease and obesity such as myocardial infarction, surgical site infection, post-operative delirium, and prolonged hospital length of stay. Such research could provide knowledge to guide more nuanced assessment of risk for those presenting to surgery with preoperative cardiometabolic comorbidity.

5.5 Conclusion

This dissertation evaluates the effect of both phenotypic and polygenic risk of cardiometabolic conditions and obesity on the development of postoperative acute kidney injury. We found three clusters of comorbidities, which follow clinical progression of these diseases. Use of renal-sparing anesthetic protocols did not significantly mediate this risk. Finally, while polygenic risk of type 2 diabetes was significantly associated with AKI, the utility of these PRS in clinical outcome models may lie in their use in place of more poorly defined phenotypes. This dissertation calls for more research on the complex interplay between cardiometabolic disease and obesity which may more fully inform who is most at risk for adverse events following surgeries.

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