

DISSERTATION

FEEDLOT HEART DISEASE: PHENOTYPIC AND GENOMIC INSIGHTS INTO
CARDIOVASCULAR REMODELING IN BEEF AND BEEF-ON-DAIRY CATTLE

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ABSTRACT

FEEDLOT HEART DISEASE: PHENOTYPIC AND GENOMIC INSIGHTS INTO CARDIOVASCULAR REMODELING IN BEEF AND BEEF-ON-DAIRY CATTLE

Feedlot heart disease (FHD), also referred to as bovine congestive heart failure, is an increasingly important cause of morbidity and mortality in cattle raised at low to moderate elevations. The objectives of this study were to determine the incidence of heart remodeling in Angus-influenced beef and beef on dairy feedlot cattle and to evaluate phenotypic relationships between heart score and economically relevant production traits. Data were collected from 4,644 cattle harvested between 2020 and 2024, including 2,453 beef cattle and 2,191 beef $\times$ dairy cattle raised at elevations ranging from 700 to 1,100 m. Heart scores (HS: 1–5 scale) were assigned at harvest using a standardized postmortem grading system. Additional phenotypes included hot carcass weight (HCW), marbling score, ribeye area (REA), backfat thickness (BF), average daily gain (ADG), and average daily dry matter intake (ADMI). Phenotypic correlations were estimated using Pearson and Spearman methods, and least-squares means were obtained from linear models that accounted for harvest date, sex, and age.

The incidence of moderate-to-severe heart remodeling ($HS \geq 3$) was greater in beef cattle (23.4%) than in beef on dairy cattle (15.4%). In beef cattle, heart score exhibited weak but significant phenotypic correlations with HCW ($r = 0.08$), marbling score ($r = -0.11$), ADG ($r = 0.15$), and ADMI ($r = 0.13$; $P < 0.05$). In contrast, heart score was not significantly correlated with production traits in beef $\times$ dairy cattle. Least-squares means revealed that beef cattle with

HS 3 had the heaviest carcasses (405.5 ± 2.4 kg), whereas cattle with HS 4 had the lightest carcasses (382.4 ± 43.0 kg; $P < 0.05$). The heritability estimates for the beef cattle were 0.23(0.05) and the estimate for the beef on dairy cattle were 0.06(0.04). These results showcase that there is a genetic component to cardiopulmonary responses in cattle. There were no identifiable genes that contributed but several significant peaks at chromosome 9, 6, 7, and 20 displayed genetic associations with growth traits found in the same SNP windows. This gave evidence that this trait is more likely polygenic and is tightly surrounded by exponential growth in these hyper responding animals.

These results demonstrate that heart remodeling is more prevalent in beef than beef on dairy feedlot cattle, not only because of the prevalence rate but also due to the lack of variability in the dataset associated with the beef on dairy cattle. Overall cardiovascular remodeling is associated with unfavorable changes in carcass merit and feedlot performance in severely affected animals. Although phenotypic relationships were generally weak, increasing severity of heart remodeling was associated with reduced carcass quality and performance, emphasizing the importance of incorporating cardiovascular health into future selection and management strategies aimed at reducing the incidence of FHD.

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Chapter 1 Introduction

Feedlot heart disease (FHD) is a severe and untreatable condition affecting beef cattle raised at low to moderate elevations. The disease results from pulmonary hypertension, in which the pulmonary artery develops lesions and vascular constriction similar to what is observed in cattle suffering from high altitude disease (HAD), but without exposure to a hypoxic environment such as is found at high elevation (Moxley et al. 2019). The limited availability of data on FHD constrains producers' ability to develop effective prevention strategies. This represents a significant challenge for the feedlot industry, as a large proportion of U.S. beef production occurs in the central region of the country, as shown in Figure 1.1. Unlike HAD, where relocating cattle to a lower elevation can mitigate the problem, no such practical management option exists for feedlot operations affected by FHD.

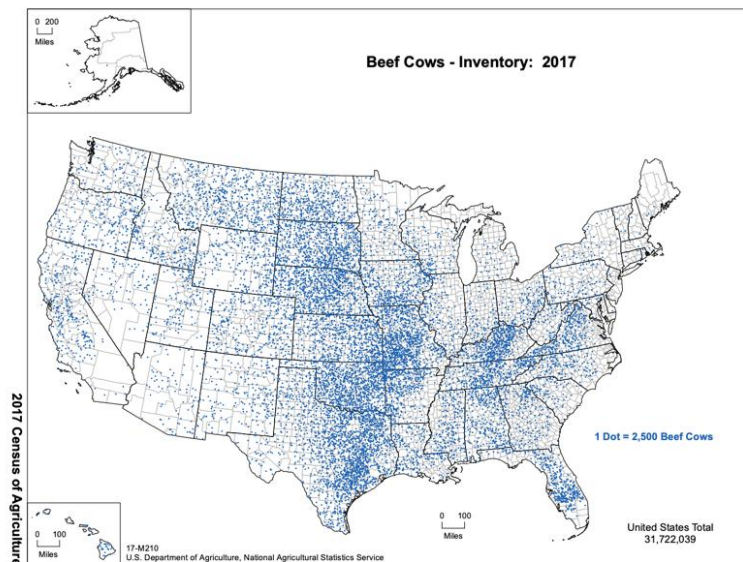


Figure 1.1: Demographic map of beef cattle in United States. Provided by United States Department of Agriculture 2017 Census.

The true magnitude of feedlot heart disease and its economic impact on the beef industry remains under investigation. A recent three-year study tracking 28,950 cohorts of feedlot cattle across 22 U.S. commercial feedlots reported that, among 75,963 total deaths, 3,282 were attributed to noninfectious heart disease (Johnson et al., 2021). Although this accounts for only about 5% of mortalities, these data reflect deaths alone and do not capture subclinical cases or complications associated with heart disease and its interactions with other conditions. Notably, Neary et al. (2015) found that cattle previously treated for bovine respiratory disease were three times more likely to die of heart failure, underscoring the interconnected nature of these health challenges. Comprehensive studies quantifying the overall prevalence of heart disease in the U.S. feedlot sector are still lacking. The USDA (2020) has estimated that a single feedlot operation may incur annual losses of up to \$250,000 due to heart failure associated with pulmonary hypertension. As a result, researchers and producers have increasingly turned their attention to pulmonary arterial pressure (PAP) as both a diagnostic and a preventive tool for pulmonary hypertension.

Pulmonary arterial pressure is measured by inserting a catheter through the jugular vein into the pulmonary artery (Holt and Callan, 2007). The trait has been shown to have moderate heritability estimates ranging from 0.26 to 0.41 (Crawford et al., 2016; Shirley et al., 2008; Speidel et al., 2019), leading to the development of PAP expected progeny differences (EPD). These EPDs were first published by the American Angus Association in 2019 and subsequently updated in 2020 for commercial use, with routine weekly updates now available (American Angus Association, 2020). Although PAP measured at lower elevations (<1,500 m) has been identified as an indicator trait for high-altitude adaptability—with a genetic correlation of 0.83 between low- and high-altitude PAP measurements (Pauling et al., 2017)—its direct application in preventing feedlot heart disease remains uncertain. To better characterize heart remodeling

associated with pulmonary hypertension, Dr. Tim Holt of Colorado State University developed a visual heart morphology grading system ranging from 1 (normal heart structure) to 5 (severe remodeling) (Holt, 2020). This system enables trained evaluators to assess the severity of heart remodeling at harvest, providing a foundation for phenotypic data collection and genetic evaluation. Heart scoring has been shown to be a relatively cheap, reliable method for graders to record pulmonary hypertension in cattle. The objective of this continued study is:

1. Evaluate current prevalence of heart remodeling in beef on dairy and beef cattle being raised in a feedlot system.
2. Update the known genetic influence of heart score through heritability estimates
3. Understand phenotypic relationships, disease manifestation, and effects on differing types of feedlot cattle.

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Chapter 2 : A Change of Heart- An Overview of Cattle Cardiovascular Remodeling

Section 1: Introduction to Cardiovascular Stress in Cattle

Beef cattle remain a vital component of the U.S. agricultural industry, playing a key role in both domestic and global markets. They contribute 17% of the \$520 billion in agricultural cash receipts, driven largely by the beef sector (USDA-ERS, 2024). About 96% of cattle come from conventional grain-fed systems, with the remaining 4% being grass-fed (South Dakota University Extension, 2023). The production process involves two main nutritional phases: backgrounding and finishing, which are crucial for optimal growth and carcass quality. These phases also induce physiological stress—backgrounding requires rapid adaptation, and finishing involves accelerated growth—leading to increased metabolic and cardiopulmonary demands. This heightened stress can predispose cattle to health issues, notably Bovine Congestive Heart Failure (BCHF), a significant cause of late-stage feeding mortality linked to cardiopulmonary stress affecting the sector comprising the 96% raised in the United States.

Research on cardiovascular stress first appeared in high altitude studies of beef cattle, where High Altitude Disease (HAD) or Brisket Disease became an increasing concern for cattle raised above 1,500 meters. The earliest mention of HAD was recorded in 1914 (Glover et al.) and described features associated with the disease in affected cattle, most notably brisket edema in severe cases. As time progressed, Jensen et al. (1974) surveyed 407,000 cattle for records of illness or early death. Nearly 2,000 cattle were necropsied, and approximately 6% showed right-sided heart remodeling as the cause of death. This growing body of information and the increasing occurrence of the disease in high-altitude cattle led to the development of measuring pulmonary arterial pressure (PAP) to assess the incidence of pulmonary hypertension in a herd

through pressure readings in millimeters of mercury. This measurement involves inserting a catheter into the jugular vein and guiding it into the pulmonary artery (Holt and Callan, 2007). The elevated pressure results from the natural constriction of the pulmonary artery in response to low oxygen levels in the blood (hypoxemia). As pulmonary vascular smooth muscle hypertrophies due to chronic pressure overload, resistance within the pulmonary artery rises. This increased afterload is transmitted back to the right ventricle, which adapts by thickening its muscular wall to maintain the forward flow of deoxygenated blood into the lungs. Over time, right ventricular hypertrophy can lead to dilation and functional failure.

As mentioned above, these cattle were originally found in hypoxic regions or high-altitude environments, where they would begin to adapt. Still, through further research, cattle raised at low to moderate altitudes, primarily feedlot cattle, are among the most at risk today. This type of congestive heart failure is known as Feedlot Heart Disease (FHD), named after the fattening of cattle it affects. These cattle raise further research questions about why heart failure was occurring in nonhypoxic environments, resulting in a similar morphology to that seen in high-altitude environments. Ultrasound technology can be used to confirm clinical signs of the disease, such as brisket edema, enlargement of the liver and jugular veins, enlargement of the pericardium, and irregular cardiac sounds, although it cannot measure the degree of pulmonary hypertension (Rauf et al. 2020). Currently, PAP is the only way to clinically diagnose cattle with pulmonary hypertension (Holt and Callan, 2007). Utilizing PAP measurements, Neary et al. (2015) examined a cohort of male Angus calves from calves to the finishing phase. The cattle received a PAP score at 6 and 18 months of age. The phenotypes of the PAP scores at 6 months for cattle with high PAP scores were the same as those cattle with high PAP scores at 18 months

of age. This predictive quality led to further questions about the utilization of PAP to uncover what was occurring in these feedlot cattle.

A veterinarian, Dr. Timothy Holt, followed cattle that received a PAP measurement into the plant to record their heart morphology. In that work, a visual grading system that categorized hearts into five scores ranging from 1 (normal) to 5 (severe) was developed as a less invasive way of collecting data on animals and their heart failure status. Over the last five years, the incidence of feedlot heart disease has continued to grow as a research topic. In 2021, Kukor et al. described sire differences in heart score within a cohort of Angus-influenced cattle, raising a positive outlook for evidence towards creating a Heart Score EPD. In 2022, the heritability of heart score was estimated to be 0.27 in Angus-influenced cattle, indicating that it is viable to genetically select for improved heart score (Kukor et al., 2022). Another study examined heart score as a binary trait; heart scores (healthy or unhealthy) were found to have a heritability of 0.356 in Angus cattle, and through breed percentage, Angus was the most positively correlated with the trait genetically (Buchanan et al., 2023). These discoveries led to the development and marketing of genomic tests that enable producers to estimate genetic risk for heart failure and mitigate it. Despite these advances in available solutions in the market, further research is needed to continue to understand the effects of cardiovascular remodeling in feedlot cattle at all stages of the heart restructuring.

Section 2: Cardiovascular Physiology

Heart Morphology:

The bovine heart is positioned within the thoracic cavity, slightly left of midline, and structurally consists of three concentric layers: the endocardium, myocardium, and epicardium. The myocardium, which contributes most towards the cardiac mass, is composed of striated muscle fibers containing cardiomyocytes. These specialized cells form the contractile units of the

heart, coordinating through the sarcomere on a beat-to-beat basis. The study conducted by Goralskyi et al. (2021) explains that the largest number of cardiomyocytes exists within the aortic ventricle, followed by the pulmonary, and the smallest are the auricle cardiomyocytes. Cardiomyocytes respond to the biochemical and mechanical stimuli from contractions of the sarcomere to determine a response on a beat-by-beat basis. These cardiomyocytes have been found to have variations that are either genetic variants or impairments and can lead to hypertrophic or dilated cardiomyopathy, calcium uptake, arrhythmias, and increased susceptibility to cardiovascular diseases (Coscarella et al. 2023). Chang et al. (2021) describe how genetic mutations in human subjects involving cardiomyocytes contribute to upregulation of proteins, causing signaling to muscular cells, causing hypertrophy or dilation dispositions. However, this system is extremely complex with several pathways; these genetic mutations could affect the heart and thus involve more research in animal studies to completely understand how to identify these variations. More difficult to separate genetic disposition to cardiovascular health, environmental stresses, whether that be cardiovascular load in response to exterior or interior oxygen levels, need to be specifically evaluated in cattle to fully discover where cardiovascular remodeling is stemming from. The research suggests that this may be on an individualistic basis, and cattle, who are already predisposed to poor respiratory mechanics, may be more likely to express these differences when placed in certain environments.

Bovine Cardiovascular Normal Pathways

The cardiovascular system has many functions, but most importantly, its responsibilities include transporting oxygen and nutrients throughout the body and exporting carbon dioxide and waste from the body. The cardiovascular system is controlled by various forces such as hormones, osmolarity, oxygen levels, and anything that could cause disturbance in the circulation

of blood through the capillaries, arteries, and veins (Chaudhry et al., 2022). The cardiovascular system maintains homeostasis through rapid, dynamic regulation of blood flow and pressure, responding in fractions of a second to internal and external stimuli. Its function, therefore, is tightly integrated with the respiratory system, forming the cardiopulmonary unit, which allows for oxygen delivery and carbon dioxide removal. The dependence between the system means that any disturbance in either will directly impact the other, with consequences for oxygen perfusion in tissue or metabolic stability (American Lung Association, 2026).

The main signaling for the cardiovascular system is controlled heavily through the central nervous system, comprised of both the sympathetic and parasympathetic systems. The sympathetic nervous system controls the fight or flight responses, resulting in increased heart rate, increased blood pressure, respiration, and gastrointestinal functions, while stress responses are activated to keep cattle on high alert. The parasympathetic system controls rest and digestion, where heart rate reduces, gastrointestinal function resumes, respiration decreases, and the cattle's overall demeanor is relaxed (Haussler, 2025). These two systems provide sensory input through neurons to produce an external response, one meant to keep the system in check, depending on the external stimulus. The external stimulus could be in response to stressful situations such as rough handling, a loud environment, the presence of a threat, or environmental factors. The environmental factor of oxygen availability in the atmosphere has a direct effect on the sympathetic nervous system, leading to increased cardiac workload to compensate for deficits in oxygen intake (Bartsch and Gibbs, 2007). In humans, the phenomenon is recorded at high altitude when hiking or residing there, or when the body is unable to utilize oxygen normally due to body mass, often known as obesity. This link to obesity could furthermore describe more of what is happening to fattening feedlot cattle.

Section 3: Pulmonary Hypertension

The heart's ability to respond on a beat-by-beat basis allows for quick reactions from the cardiovascular system to respond to stress or excitement. These responses can increase blood pressure, create vascular dilation or constriction, and increase blood flow to maintain homeostasis. The same mechanisms exist in cattle; however, cattle are particularly sensitive to the development of pulmonary hypertension. In the beginning stages, pulmonary hypertension is reversible, but with further progression, its results are permanent and deadly to cattle and are not restricted to a particular altitude. Pulmonary hypertension describes high blood pressure in the pulmonary artery, and due to the amount of force needed to move blood to the lungs to be reoxygenated, the artery constricts and narrows. Overall, when the cardiovascular system fails to maintain equilibrium, cardiac output decreases, and venous blood begins to pool, increasing the hydrostatic pressure in the systemic and pulmonary vessels. This fluid then enters the tissues, causing edema throughout the body, most notably around the jaw and brisket. The presence of this fluid begins to enter the lungs, causing intrapulmonary shunting: oxygen exchange attempts are made through fluid-filled or collapsed alveoli. As the body tries to compensate, these non-ventilated areas begin to receive blood but are unable to exchange the carbon dioxide for oxygen, and deoxygenated blood reenters the system. Once the pulmonary artery and arterioles constrict over time, they begin to lose compliance to expand. This is vital to allow the volume of blood to flow through. A compliant vessel will expand easily as pressure increases, while a non-compliant vessel will be stiff and rigid causing pressure to increase further. This process explains the close physiological links between the heart and lungs, creating a feedback loop between pulmonary hypertension and progressive shunting. Ultimately, the hypertrophy once experienced fails, and myocardial walls weaken, decreasing regulatory control of blood pressure and ensuring heart failure in severe cases.

The catalyst for this condition is complicated, and little is known about what causes some cattle to have hypersensitivity to stresses that induce this phenomenon. Historically, pulmonary hypertension disease was recorded as brisket disease or High-Altitude Disease. (HAD) which described the instance of pulmonary hypertension occurring in cattle at >6,000 feet in altitude (Thomas et al. 2015). In cattle raised at altitude, the catalysts of pulmonary hypertension are attributed to the lack of oxygen availability. In humans traveling to extreme altitudes, the Center for Wilderness Safety describes that oxygen is in the atmosphere at 20.9% at any altitude. Still, due to Boyle's law, as pressure decreases, fewer of these molecules are present, contributing to the term "thinner air". For hikers, the Center for Wilderness Safety explains that the human body can acclimate to cope with low oxygen levels if precautions are taken. However, if done incorrectly, it can lead to high-altitude pulmonary edema, cerebral edema, and/or acute mountain sickness. Cattle, unlike humans, are less efficient at this acclimation process. Once they begin to respond to alveolar hypoxia in the lungs due to the low oxygen molecules readily available, they often cannot compensate due to their biological disadvantages in lung size and function.

Feedlot systems demonstrate similar patterns of cardiopulmonary failure in low to moderate altitudes, where the hypoxemia captured cannot be fully explained by atmospheric oxygen limitation. Instead, evidence suggests a multifactorial etiology describing rapid weight gain, altered body to organ mass ratios, metabolic inflammation, and genetic susceptibility. The condition, FHD, is now a leading cause of late-stage feedlot mortality and a substantial burden to U.S. beef production.

Pulmonary Arterial Pressure

Pulmonary Artery Pressure, PAP, is utilized as a selective tool in identifying animals at moderate to high risk of pulmonary hypertension, a catalyst of progressive BCHF, or as an

identification for predisposition to high altitude disease. PAP scores have been used for these conditions for several years in order to curb the frequency of BCHF in fattening cattle, but the collection of information also contributes to a wide variety of research that encompasses an understanding of where the problems arise for fattening cattle. As research shows, calves at high altitude with signs of moderate to high pulmonary pressure at a younger age lead to cattle with even higher pulmonary pressure during the finishing phase (Neary et al. 2015). PAP research was taken one step further in 2016, where fattening Angus cattle were phenotyped to be either Low or High PAP. Tissue samples were taken from the right ventricle, aorta, and pulmonary artery of these animals to identify any tissue specific variants. Through this analysis, 139 SNPs were deemed key regulator genes within the involvement of high-altitude disease, or BCHF (Canovas et al., 2016). Although it will not be feasible to utilize or expose PAP scores as a selection measurement to every producer, their importance ranking resides within individual animal breeders.

When examining PAP measured at different elevations, the phenotype itself may not even have the same genetic interaction either. Recorded PAP measurements at moderate elevations (1,600m or less) were compared to measurements from high elevations (greater than 1,600 m). Using a bivariate animal model, elevation was not seen as a significant factor to PAP variability within the differing elevations. Both heritability estimates were considered moderately heritable at both high and moderate elevations. This study did reveal that PAP scores at different elevations may not be related. There can be the use of PAP measurements at higher moderate elevations to produce an EPD for one elevation, and a separate EPD for another. This would show which animals may be at less risk for pulmonary hypertension at moderate elevations but identify individuals that may not do well if moved to a higher elevation. This separation between

elevations within an EPD allows for better management of individual animals in geographical at-risk locations (Pauling et al., 2018; Speidel et al., 2021). These findings were further investigated in 2020 through the estimation of correlations between bulls across the elevations and ages. Cattle received multiple PAP scores at different ages and elevations and included breed as a factor of both Hereford and Angus bulls. The interaction between elevation and age, as well as the breed, had a positive association with the variation within PAP predictability. The yearling PAP measurements collected at moderate altitude were correlated with high altitude PAP measurements for the same individuals (Zimprich et al., 2020). The differences between yearling and weaning weight PAP differed when measuring PAP score at altitude. The study supported the findings that yearling PAP can be indicative of how cattle perform at altitude than the predictability of only using weaning age PAP. This relationship of higher PAP in growing cattle at altitude is shown when following calves born at moderate/high elevations compared to calves born at lower elevations. The calves raised at higher elevations showed a significant increase in their mean PAP scores, comparatively, calves at moderate elevation did not experience this same trending progression. Findings showcased the mean PAP score increasing with age are positively associated with the 13 altitude the calves are raised in (Neary et al., 2015). Calves growing at high altitudes ($>2,170\text{m}$) had their mPAP scores increase as they aged. Adversely calves raised at moderate altitudes ($1,470\text{m}$) did not have an increase in their mean PAP scores as they aged. Based on the results, PAP scores would be associated with the altitude at which the cattle are born and raised at, specifically seen as the cattle increase in age. This would signify those cattle at this higher altitude may experience increases in their PAP score as they grew larger and got older. This also may present itself as one of the risk factors of moving cattle from moderate altitude to high altitude. PAP as a selection tool for bulls to pass on their low PAP scores to their

offspring is a hopeful step in decreasing the incidence of BCHF. There are multiple facets of PAP score that make it inaccessible for many producers to utilize due to time, cost, and accessibility. Collection of phenotypic PAP data is costly, time consuming, and can range from \$10 to \$17 per test (Gjermundon, 2000). The need for a veterinarian to perform the procedure is one more veterinary visit, and one more time cattle need to be brought up to a secure chute area. These issues make finding relationships between PAP and less invasive techniques beneficial. Human cardiovascular research has suggested that increased body fat percentages increase a person's risk of cardiovascular diseases (Littleton et al., 2017). The same idea carries over to bovine research where body fat distribution in cattle would be indicative of their PAP score and the other pressure readings taken in the heart. Pressures were taken in a cohort of crossbreed beef animals in the finishing stage, six days before harvest in a study done by Freeman et al in 2016. The body measures included KPH (Kidney, Pelvic, and Heart Fat) percentages, USDA quality grade, empty body fat, and 12th rib fat thickness. PAP and central venous pressure were significantly, positively associated. Keeping mean PAP scores controlled, central venous pressure of animals with 2% KPH had a higher-pressure measurement than animals with a KPH of 1.5 %. These findings were significant ($P < 0.01$) and showed that as fat around the pelvic, kidneys, and heart increased, the higher the pressure. No other body fat measurements including USDA quality grade, empty body fat percentages, and fat thickness over the 12th rib were found to be significant (Freeman et al., 2016). Fat percentages may be beneficial in having a correlation with central venous pressure because central venous pressure has a relationship to PAP. Unfortunately, but with no other strong correlations of other body fat measurements and a small sample size of crossbred animals, more research needs to be done in high altitude and breed specificity.

A major takeaway from Freeman et al. (2016) is the utilization of the relationship between fat and central venous pressure, which provides an explanation of why higher pressures are prevalent during the finishing period as more fat encases the heart and cardiovascular system. Predicting PAP and the adaptability of cattle has become the next step in PAP research and development. Cattle have been shown to adapt in a variety of ways. One way specifically to adapt to the high altitude is by increasing respiration rate. Increasing respiration rate allows for a more frequent exchange of oxygen and carbon dioxide in the body in response to the oxygen scarcity in high-altitude environments. Although oxygen may be entering the body at a more frequent rate due to the animal's attempt to adapt, Gullick et al. (2016) presented that this sign of a physical adaptation does not necessarily aid cattle in obtaining a greater oxygen/carbon exchange as efficiently as the cattle would be in low altitude settings. Their research found that because the hematocrit or red blood cells within the body does not increase, cattle still show signs of hypoxemia and hypocapnia despite the body's active role in attempting adaptation.

Body Weights Effect on the Cardiopulmonary System

Obesity is defined by the World Health Organization as excessive and abnormal fat accumulation, relative to sex and height, that poses a health risk to the individual (WHO, 2023). Risk is commonly quantified using the body mass index (BMI), where an increasing fat proportion corresponds with a higher risk of disease. Obesity is a major risk factor for cardiovascular disease, including myocardial infarction and stroke, as well as endocrine disorders such as type 2 diabetes (Cornier, 2022). The pathophysiology of obesity-related heart failure in humans is strongly associated with hyperglycemia and hyperinsulinemia, which promote systemic inflammation, maladaptive myocardial remodeling, and ultimately progression to heart failure (Horwich and Fonarow, 2010).

Although there are no studies measuring insulin resistance in feedlot Angus cattle, evidence from Nellore bulls fed high-concentrate diets indicates that prolonged feeding (up to 108 days) increased insulin sensitivity while elevating inflammatory markers, suggesting that diet-induced metabolic inflammation could contribute to cardiovascular strain in feedlot cattle (Sousa et al., 2022). This highlights the potential for parallels between human obesity-related cardiometabolic disease and diet-driven inflammatory responses in cattle.

Major organizations, including the American Heart Association, label obesity as a chronic disease that can be treated through lifestyle changes such as reducing body weight through decreasing caloric intake, exercising, and, potentially in severe cases, short-term medication or surgery. Humans have direct agency over these lifestyle factors, but livestock do not. Nutritional intake and energy balance in cattle are primarily determined by management decisions, where feeding strategies are designed to maximize growth efficiency and carcass quality rather than long-term health.

In livestock, the evaluation of obesity is complex. Cattle are genetically selected for traits that promote both muscling and fat deposition to optimize carcass yield and marbling under intensive feeding conditions. While body condition scoring (BCS) is a widely used tool to assess energy reserves in cattle, it does not capture the physiological consequences of selecting for rapid fat and muscle within a feedlot system. Thus, some similarities can be drawn between human obesity and feedlot cattle phenotypes: both represent states of increased body mass that place disproportionate amounts of metabolic and cardiopulmonary demands on the individual. However, in cattle, these traits are economically desirable and biologically tolerated over a shortened lifespan, whereas in humans, they are detrimental to long term health. More importantly, biological disadvantages may arise less from BMI equivalence in cattle and more

from intrinsic anatomical limitations, such as the ratio of body mass to lung capacity, which could contribute to cardiopulmonary disease risk in intensively finished animals.

A biological disadvantage hypothesized to predispose cattle is the disparity in lung and heart size ratios. When compared to horses, a species of similar weight and size, horses have lower respiration and a lung capacity that is significantly larger (Gallivan, 1989). These differences between species can be seen in heart rate (horses: 28-40 beats per minute, cattle: 40-70 beats per minute). This means horses, on average, have a heart that can move the same amount of blood with less work. Respiration rate reveals that horses only need to take 8-16 breaths per minute, while cattle need anywhere from 10-30 breaths. The advantage of oxygen exchange is apparent in these vital signs, but it is also evident that horses are more athletic than cattle, which spend energy on growth rather than on movement (Le Viness. 2018). While horses are bred for completely different purposes, dairy cattle are a much closer comparison to their beef counterparts. Although there are limited studies currently on the relative weights of organs between beef, dairy, and beef on dairy, the selection differences between the breeds could showcase issues for cattle that are heavier because of muscling and fat rather than stature. One breed could be considered tall and lean in dairy cows, while beef cows tend to bulk and focus on fat deposition, fat that could ultimately encase the heart and other vital organs.

In humans, obesity reduces pulmonary function primarily through increased thoracic and abdominal mass, which restricts chest wall compliance, reduces total lung capacity, and lowers expiratory reserve volume (Littleton, 2012). These mechanical constraints increase the work of breathing and accelerate the respiratory rate to maintain oxygen uptake and carbon dioxide clearance. In advanced cases, regional hypoventilation produces hypoxemia, and severely compromised alveoli may be excluded from gas exchange altogether, creating further

inefficiency in oxygen delivery. The resulting hypoxic environment imposes sustained biological strain on the cardiopulmonary system. This creates a hypoxic environment within the body that the body must now overcome. Comparable mechanisms are thought to occur in cattle. When systemic oxygen levels decline, pulmonary shunting redistributes blood flow toward well-ventilated lung regions. However, persistent ventilation-perfusion mismatch prevents full equilibrium of gas exchange, producing chronic hypoxemia and progressive cardiac overload. These physiological pressures may contribute to the high prevalence of bovine congestive heart failure observed in modern feedlot cattle.

In a comprehensive literature review, the relative organ weight was averaged across the available literature before 2020. The average percent of body weight for beef cattle, including Angus and Hereford, was 12.8% for adipose tissue, 0.43% for heart mass, and 0.85% for lung mass. In dairy cattle, primarily Holstein and Jersey cattle, the masses are as follows: 13.21% for adipose tissue, 0.37% for heart mass, and 0.68% for lung mass. Notably, female beef cattle exhibited significant differences in lung size, having smaller lung proportions to body ratio and a larger ratio of adipose tissue (Lin et al., 2020). Such anatomical differences suggest that genetic selection for growth and carcass yield may indirectly influence cardiopulmonary vulnerability.

The integration of beef sires into dairy breeding further complicates predictions on carcass size and composition, as organ scaling remains relatively similar (Swett et al., 1939). A study estimating the mean breed effects of beef sires on dairy dams concluded that breed differences amongst beef sires resulted in large variability within carcass traits and calving intervals. The study examined close to one million individuals and their calving phenotypes. Of these, 103,000 had carcass trait information, and a smaller subset of 80,000 had price data. Calves from Angus bulls had the shortest gestational length on average compared to other beef

breeds, 282.3 days. Angus calves are also sold for the lowest amount compared to the other breeds of Charolais, Limousin, Belgian Blue, Hereford, Simmental, and Salers. All beef breeds were slaughtered 22 days on average earlier than Holstein sired calves, with Angus and Hereford both on average slaughtered 9 days earlier than other beef sired progeny (Berry et al. 2023). These findings highlight the influence of breed on production efficiency and, potentially, on organ to body mass allocation, which may be relevant for evaluating susceptibility to cardiopulmonary disorders.

Despite these differences, the cardiovascular system is anatomically conserved across breeds, consisting of a single heart and paired lungs supported by a vascular network. The challenge, therefore, lies in identifying the catalysts that trigger disproportionate sensitivity to cardiac failure in certain cattle populations. Current evidence suggests that management factors, genetic selection for rapid growth rate, and altered organ to body mass ratios collectively contribute to cardiovascular strain, but knowing which factor increases the sensitivity to the strains can only be explained by determining differences in the genetics of the cattle. Overall, BCHF remains a difficult and economically significant disease. Its impact is compounded by the inability to treat affected animals effectively and challenges in early detection, suggesting increasing prevalence in the cow-calf and feedlot systems (Herman, 2024). These factors showcase the urgent need for integrated genetic, nutritional, and management strategies to mitigate cardiovascular risk in both beef and beef-x-dairy cattle.

The Respiratory System of Cattle:

The bovine respiratory system consists of the nasal passages, trachea, bronchi, bronchioles, and alveoli, functioning collectively to maintain gas exchange while providing mechanical, cellular, and secretory defenses against pathogens. Comparative anatomical

differences across species influence respiratory efficiency and disease susceptibility. For example, cattle possess relatively small lungs with low tidal volume, a characteristic that, combined with their high metabolic oxygen demand, renders them highly sensitive to environmental stressors and predisposed to pulmonary hypertension (Tonozzi, 2024). Structural constraints in the cattle also impact pathogenic dynamics.

The Farmed Animal Antimicrobial Stewardship Initiative notes that cattle are predisposed to developing respiratory diseases due to their high respiratory rate and limited lung reserve, which promotes pathogen retention deep in lung tissue, leading to an elevated prevalence of respiratory infections compared with other livestock species. In 2013, the USDA found that 16.3% of feedlot cattle exhibited clinical signs of respiratory disease during the feeding period. Out of this group, 87.5% of the cattle were treated with some form of antibiotics, and due to this direct cost, respiratory disease is extremely costly to feedlot systems, as each case amounts to ~\$23.00 per head (APHIS, 2013). This monetary value does not account for the loss of death cases and the decline in feedlot performance over treatment periods. Overall, considering these disadvantages and the prevalence of disease within the respiratory system, the close link between the lungs and heart highlights the complexity of the pulmonary connection and the interaction between cattle respiratory health and cardiovascular health.

Section 4: Feedlot Heart Disease

Feedlot Heart Disease (FHD) is a form of right congestive heart failure affecting feedlot cattle, causing irreversible cardiovascular and pulmonary damage in the most severe cases. In 2023, 75,963 feedlot cattle died over three years within the 22 US commercial feedlots surveyed in this study (Johnson et al. 2023) Out of this subset of feedlot cattle of varying commercial breeds, 3,282 cattle died of non-infectious cardiovascular disease, otherwise known as

congestive heart failure. These cattle comprised 4% of the overall early feedlot deaths. Examining the multiple probabilities of occurrence differed between sexes, increased cohort sizes, and days on feed, the Timing of heart failure, on average, occurred at 110 d on feed. Previously, in 1976, Jensen et al. found the incidence of heart failure was 2.85 head per 10,000 animals. This led to a study in 2015 looking at the prevalence of FHD in feedlots within the United States and Canada. This study reported a doubling of the incidence of FHD from 2000 to 2012, but incidences still occurred around 4 months of feeding. Cattle treated for BRD were also three times more likely to die from heart failure compared to those who were never treated (Neary et al. 2015). This becomes more concerning as cattle enter the finishing phase during this period.

The finishing phase is where cattle begin to eat a higher grain diet, allowing them to put on heavier muscling as they approach harvest and begin depositing more intramuscular fat within their muscular tissue to add marbling. The finishing phase is crucial for developing cattle to a mature harvest weight, and often cattle are the most valuable and the most at risk for economic loss if not finished correctly. Oklahoma State University Extension describes four realistic examples to take into consideration when finishing cattle: steers typically are more efficient than heifers, lighter calves entering the finishing phase take longer than heavier starting weights calves entering the finishing phase, keeping fat thickness constant larger framed cattle will always have higher finishing weights and calves finished on pasture will have lower marbling, dressing percentages, and gains compared to cattle finished within a dry lot (New et al. 2020). This creates an intensive feeding period where these goals affect the end profits and are critical to beef entering into the feeding sector. In 2011, the USDA reported the prevalence of Bovine Respiratory Disease (BRD) was present in 16.2% of the cattle within the United States and 96%

of the feedlots reported some case of post weaned calves with BRD upon arrival (USDA, 2011). Similarly, the mortality loss due to the disease was reported in 2017 to be \$907.8 million in economic loss just due to mortality results (USDA). The established connection between both diseases makes it difficult to deduce if heart failure became a factor, as we continue to expect an increase in incidence rate if no mitigation occurs. Ultimately, it causes severe economic loss to the beef industry in the form of early feedlot death and decreased performance and carcass characteristics if not mitigated and managed through genetic selection and preventative mating decisions.

Maintaining and mitigating early feedlot death due to BCHF has become a rising concern throughout the past several decades. Particularly when there is an influence of disease that is untreatable and fatal, which leads to minimal options in cattle health management. Overall, the main concerns stem from the economic loss and animal welfare questions. The USDA Cattle & Beef- Market Outlook predicts that in 2025, projected beef production is expected to be 26.565 billion pounds in the United States, of which 2.795 billion pounds are available for exporting. In the United States, the last recorded cattle population included 87 million beef, dairy, and exotic breeds such as water buffalo. As of 2024, the total number of beef cattle has fallen by 2%, resulting in 28.2 million beef cattle residing in the United States. Ideally, all these beef cattle and even dairy cattle will eventually enter the food production chain. However, when there is a large enough population size, even small percentages can result in millions of dollars lost in only one disease or circumstance. This is evident when Bovine Respiratory Disease (BRD) costs American feedlots \$800 to \$900 million in revenue annually. This is between treatments, clinical signs affecting feedlot performance, lung lesions, and pleural lesions. Catching BRD early is expected to reduce the economic impact of this disease, which can also aid in the mitigation of

BCHF (JAS, 2020). There is currently no known economic impact predicted for 2025 beef cattle, but the USDA predicts that, at a minimum, the disease will cost the beef industry \$250 million annually. This economic impact is expected to increase as Neary et al. (2015) reported that the incidence rate of fattening feedlot cattle between 2000 and 2012 doubled in prevalence and that cattle treated for BRD were three times more likely to die of BCHF. The heart and lungs make up the cardiopulmonary system, and without a proper necropsy at death, it is difficult to rule out which disease ultimately caused early feedlot death. But considering these diseases are so closely linked, it is impossible to emphasize BRD and not BCHF. Overall, scientists and economists can agree that cardiopulmonary system dysfunction will be detrimental to the supply chain if not prevented, but the difference is that BRD can at least be treated, while BCHF needs to be looked at primarily from a selective breeding and genetic lens.

Section 5: Heart Scoring

Heart scoring is a visual grading system developed by Dr. Tim Holt at Colorado State University to categorize hearts by the degree of remodeling based on physiological changes. This “scoring” is completed at harvest or at necropsy for a less invasive method of determining an animal’s disease progression. This system has been used to identify cattle that experienced feedlot heart disease and were harvested. The ease of collection involves a person that has been obtained training and certification in heart scoring and occurs at the gut table, prior to USDA inspection. This allows hundreds of cattle to be collected in hours, versus PAP measurements, which can take 2+ minutes per head. The scale of the system ranges from 1 to 5, representing hearts that exhibit no remodeling to those exhibiting severe remodeling. Figure 5.1 provides a visual of the grading system used. Normal hearts are scored 1, and gradually as the scores increase, differences in the right ventricles, left ventricular apex, and pulmonary artery can be

seen until muscle weakness in grades 4 and 5 showcases right ventricular wall caving in, ventricular muscle collapse.

As the degree of remodeling increases, higher pulmonary arterial pressures cause the remodeling in the first place while the cattle were alive. It is not understood how quickly some cattle experience hypertension and then begin to remodel. In preliminary studies, the relationship between heart score and PAP was positive, indicating this relationship of the two traits captures the cardiovascular stress (Heffernan, 2020). The research continued at Colorado State University, where the next step was to determine if there was a genetic component to heart scores. A cohort of Angus-influenced cattle was examined, each with known sire information and heart scores. Using a linear analysis, sires were found to have a significant influence on their progeny's heart scores, meaning some sires were more prone to producing progeny who experience moderate to severe remodeling (Kukor et al. 2021). From there, heart scores were examined to look at the heritability estimate of Angus-influenced feedlot cattle, and it was found to be 0.27, suggesting a potential for genetic selection utilization like PAP (Kukor et al. 2022). In commercial fed cattle, the heritability of heart score was found to be 0.356, adding more evidence that the development of an EPD is possible (Buchanan et al., 2023). The prevalence of abnormal hearts was ~30% in these two studies. Most recently, a study found 106 individuals out of 346 feedlot deaths had evidence of cardiac enlargement and misshapen ventricles with no signs of other infectious diseases. They also recorded that these cases had increased heart widths, thinner left ventricular walls, and enlarged right ventricular lumen areas (Long et al., 2025). These results are expected due to what is known about heart remodeling, but it is one of the few studies that were able to measure these findings.

Section 6: Avian Studies in Cardiovascular Right-sided Heart Failure

Much of the information known about right-sided heart failure in cattle comes from high-altitude studies, but with feedlot heart disease occurring at low to moderate altitudes, the growth factor can be seen through the history of broiler chickens as answers to the problem. Broiler chickens are particularly interesting because they have been selectively bred with goals like those of beef cattle: rapid growth and carcass-specific traits. Standard growth broilers now achieve a feed conversion ratio (FCR) of 1.57 kg feed per kg body weight and reach a market weight of approximately 3 kg within 45 days (Zhou et al, 2024). Likewise, the beef industry has increasingly focused on improving genetic potential for growth, complementing these efforts with high-energy, grain-fed diets during shorter, intensive finishing periods. Figure 2.1 illustrates the progression of broiler chicken growth over time at various production stages. This not only demonstrates the impact of intensive selection on enhancing breast muscle yield to satisfy consumer demands, but also parallels the trajectory seen in beef cattle breeding and production systems.

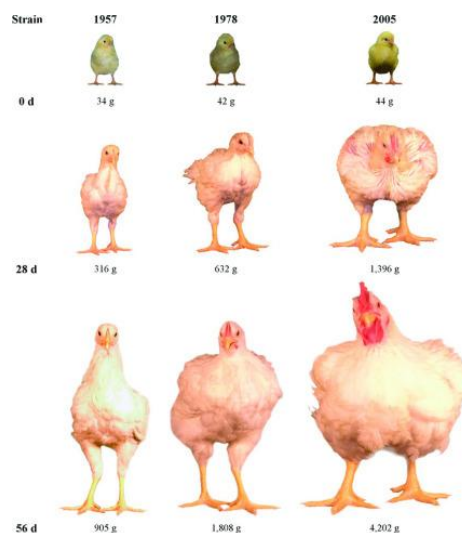


Figure 2.1 Broiler chickens' growth by days provided by The University of Alberta Meat Control. Zuidhof et al, 2014.

Figure 2.2 illustrates the beef cattle production cycle, in which animals are either traditionally finished on pasture or in feedlots. The primary distinction between these systems lies in the time required to reach market weight. Unlike broiler chickens, cattle do not exhibit large disparities in body size due to their finishing method; however, the rate at which they reach target weights differs significantly. Feedlot finished cattle typically undergo a 4–6-month intensive feeding period, whereas pasture finished cattle rely on forage quality and generally require 6-10 months to complete the finishing phase. Despite the extended period, pasture-finished animals often achieve lower final weights compared to their grain-fed counterparts, reflecting growth efficiency challenges that parallel findings in avian production research.

Rapid growth in broilers has also been linked to cardiac complications. An early study found that 289 out of 925 broiler chickens exhibited right ventricular remodeling by 48 days of age. Interestingly, these birds were also heavier at both 14 and 28 days of age. Researchers then selected a subset of 259 chickens to continue feeding until 16 weeks of age before harvest. During this period, 3.5% of the chickens experienced early mortality, 26% died between weeks 7 and 16, and 10% showed right-sided cardiac dilation at 16 weeks, indicating severe heart remodeling. This study, published in 1987, highlights the physiological cost of rapid growth in

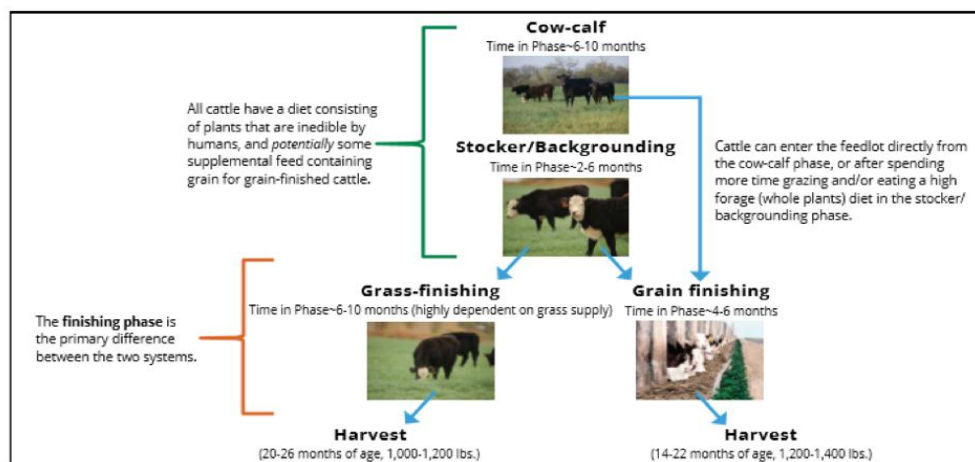


Figure 2.2 Cattle Life cycle with differing finishing phases. Photo provided by Beef Research Fact Sheet. Broocks et al. OSU.

broilers. As shown in Figure 2.1, the modern broiler has undergone even more dramatic genetic and production-driven changes since then, further intensifying these physiological challenges (Julian et al. 1987). Although both species differ significantly in weight and size, the proportions and ratios of body mass to heart capabilities illustrate the devastating impact of the disease if not properly addressed in the next generation.

Avian studies have also shown the impact of environmental and dietary stressors on cardiac function. Heat stress has been shown to play a crucial role in compromising cardiac function, particularly in fast-growing broilers with relatively small heart-to-body size ratios. Under heat stress, both heart weight and body weight decreased significantly in these birds, whereas slow growing broilers did not exhibit the same reduction, suggesting greater resilience and leading to selective heat tolerance breeding efforts (Zhang et al., 2017). Although heat tolerance and its direct impact on cardiac morphology have not been extensively studied in cattle, similar physiological challenges could arise when a compromised heart struggles to regulate blood flow efficiently under thermal stress. In a study by Miraslimi et al. (1993), one week old broiler and Leghorn chicks were given drinking water supplemented with 0.5% salt. The leghorns showed minimal adverse effects, while the broilers experienced a 50% mortality rate due to pulmonary hypertension induced right heart failure and a 32% reduction in growth rate. While cattle are unlikely to be affected by these specific factors to the same extent, the complexity of cardiac dysfunction in livestock presents challenges in identifying at risk animals. Avian research thus underscores the need for further investigation into comparable physiological stressors in feedlot cattle to better understand and mitigate causes of unexpected death.

Overall, both poultry and cattle illustrate how selective breeding and intensive production practices aimed at enhancing growth efficiency can create unintended cardiovascular risks. Avian

research provides a model for understanding these risks and the importance of exploring similar mechanisms in beef cattle to improve health outcomes and production efficiency.

Section 7: Conclusion

The adverse effects of heart remodeling on the productivity and profitability of the beef industry, specifically for genetically superior feedlot cattle, can be mitigated with genetic selection for cardiovascular fitness. Many options are available on the market to begin genetic testing of herds that may be predisposed to the disease and encourage the use of genetics when making selection decisions. Cardiovascular remodeling is not treatable and, for that reason, has a heightened economic relevance across the cattle industry, positioning the complex issue as a cattle health and welfare concern at any altitude. Building on the success of PAP selection, heart scoring offers a promising strategy to reduce cardiovascular risk through genetic mechanisms.

Heart scores and its relationship to heart disease could also continue to provide answers to other health challenges in the industry, such as bovine respiratory disease. Other livestock provides insight into what could occur in cattle and why cattle have begun to experience these challenges at an increasing rate. While advancing our understanding of heart-related traits will not eliminate the risk of heart remodeling completely due to the multifactorial causes, it is likely to reduce its impact on cattle production and industry profitability.

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Chapter 3 : Phenotypic Relationships Between Heart Scores and Economically Relevant Traits

Introduction

For feedlot cattle experiencing pulmonary hypertension at low to moderate altitude (below 1,500m), there is limited information on phenotypic differences in the late stage of heart remodeling. Moreover, there is even less information on the incidence rate of FHD of beef-on-dairy progeny and the potential risk of heart failure. This disease, known as Feedlot Heart Disease (FHD), is more broadly known as Bovine Congestive Heart Failure (BCHF), and is the direct consequence of the heart's inability to efficiently transport deoxygenated blood for gas exchange and oxygenation. This imbalance triggers compensatory mechanisms, leading to phenotypic differences in heart shape and morphology. Evidence suggests that heart failure in feedlot cattle is increasing in prevalence, whereas historically it represents a relatively minor contribution to feedlot mortality. In a 2023 study, the incidence of severe cardiac remodeling in commercially fed cattle at harvest was reported to be 4%; this estimate did not include cattle exhibiting moderate remodeling (Buchanan et al., 2023), suggesting that the total burden of structural cardiac change may be underestimated.

Similar findings were reported in a large-scale investigation by Johnson et al. (2023), which evaluated 13 feedlots across the United States and Canada at elevations <1,500 meters. In that study, total death loss attributed to right-sided heart failure was 7.8 per 10,000 head of cattle. The risk of incidence increased with elevation, and beef cattle exhibited greater susceptibility than dairy and dairy-cross cattle. Additionally, cattle previously treated for bovine respiratory disease (BRD) died from heart failure 11 days earlier than untreated cohort mates. Dairy-cross cattle that succumbed to heart failure died approximately 37 days earlier in the feeding period

than beef cattle, indicating potential breed-related differences in disease progression or physiological tolerance (Johnson et al. 2023). Earlier work by Neary et al. (2013) further demonstrated that right-sided heart failure can occur in young calves, with pulmonary hypertension present in approximately 50% of calf mortality cases. Collectively, these findings indicate that pulmonary hypertension and subsequent cardiac remodeling are not restricted to high-altitude systems or late-stage finishing cattle but may represent a broader and increasingly relevant health concern across production stages.

A complication of the disease is that symptoms typically appear only in very severe cases and can be difficult to distinguish from those of other diseases, such as pneumonia. In order to confirm heart failure cases in early feedlot death, a necropsy would be required. This decision would be to the discretion of production management and may or may not occur, and therefore unaccounted for in the known true prevalence of the disease (Moxley et al., 2019). Previous studies on feedlot cattle reported that cattle with heart remodeling, who did not experience early feedlot death, accounted for ~30% of the herd (Kukor et al. 2021). Cattle with severe remodeling are linked to high pulmonary arterial pressure (PAP), which is associated with negative performance and carcass quality. In a study of high-altitude growing steers, heart scores of 4 were associated with the highest PAP scores, lowest carcass weights, and lowest overall weight gain (Heffernan et al., 2020). Similarly, heart scores reflect cardiac remodeling in cattle raised at any altitude, but were primarily developed for cattle raised at low to moderate altitudes to provide a tool for recording feedlot cattle pulmonary hypertension. While high altitude disease is driven by chronic atmospheric hypoxia, feedlot heart disease occurs without environmental oxygen restriction. Nonetheless, current evidence suggests that a hypoxic event may still trigger pulmonary hypertension in these systems, though the underlying cause of that hypoxia remains

unknown. In beef cattle, more recently, a subset of fattening feedlot cattle at a moderate elevation (1,080m) was found to have a 27% incidence of moderate to severe remodeling at harvest (classed as 3 to 5 heart scores), while beef-on-dairy cattle had an 11% incidence rate (**Kukor et al. 2023**). The continued increase in the incidence rate at these lower elevations does not include those who experienced early feedlot death; it only captures those with evidence of heart remodeling at harvest. Based on PAP research, the heart score needs further evaluation of phenotypic effects due to heart remodeling in feedlot cattle. Therefore, the objective of this study was to determine, using a larger sample of fattening feedlot cattle, an updated incidence rate for beef and beef-on-dairy cattle raised at altitudes between 700 and 1100 meters, and to describe phenotypic differences across heart score categories.

Materials And Methods

Animal and Data Collection

Data were collected on cohorts of fattening feedlot cattle in Canyon, TX, and Montezuma, KS, between 2020 and 2024. This study included steers and heifers from both locations, all of which were Angus-influenced. All cattle were fed finishing diets. In the data, 2,453 beef cattle and 2,191 beef-on-dairy cattle were evaluated for heart score. There were 1,238 steers and 1,215 heifers in the beef sample and 304 steers and 1,887 heifers in the beef-on-dairy sample. Heart score (**HS**), Backfat (**BF**), Marbling Score (**Marb**), Ribeye Area (**REA**), Hot Carcass Weight. (**HCW**), Average Daily Gain (**ADG**) and Average Dry Matter Intake (**ADMI**) were provided at varying degrees depending on the type of cattle. Lots were of a uniform sex, harvest date, and similar managerial style within each feedlot.

Cattle were harvested at various plants in the panhandle of Texas and in southwest Kansas. Carcass data were collected at harvest along with heart scores. Heart scoring was

performed using the visual grading system developed by Dr. Timothy Holt, DVM, at the Colorado State Veterinary Teaching Hospital. The visual grading system is shown in Figure 4, and the descriptions are found in Table 3.1.

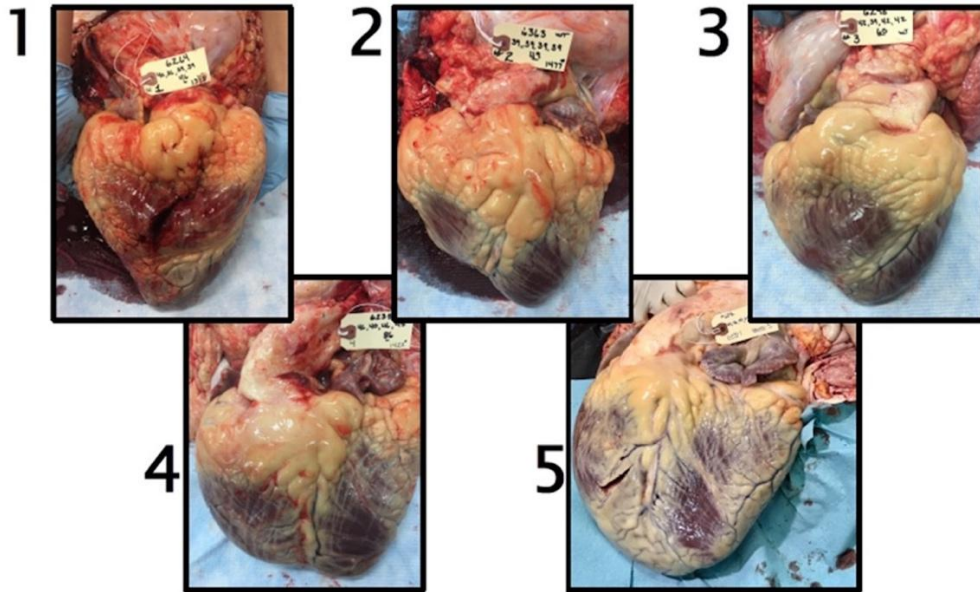


Figure 3.1 Heart scoring visual grading system created by Dr. Time Holt DVM, Colorado State University.

Table 3.1 Description of heart scoring system for visual grading Kukor et al. 2023

Score	Description
1- No Change (Healthy)	Normal conical shape, right ventricle smaller than left, normal pulmonary artery, no vessel wall thinning
2- Mild Change (Healthy)	Normal conical shape, right ventricle becoming pronounced, enlargement of pulmonary artery, losing apex point, no vessel wall thinning
3- Moderate Change (Unhealthy)	Beginning to lose conical shape, right ventricle larger than left (reverse D shape), thinning of vessel walls, pulmonary artery enlarged, blunting of apex
4- Severe Change (Unhealthy)	No conical shape, no apex due to rounding of right ventricle, dark spots on pulmonary artery, cardiac muscle becoming softer
5- Severe Change (Fatal)	Heart completely flaccid, right ventricle extremely pronounced, very enlarged pulmonary artery, no muscle tone, heart was flat.

Heart scores were captured by visual graders utilizing these criteria, with each lot scored by a single individual. There was a total of 130 sires represented in the dataset, with 23 sires overlapping between the groups. Sires ranged from 1 to 608 in number of progenies.

Statistical Analysis

The data were analyzed using RStudio. All phenotypes were organized, and data were cleaned to only utilize cattle with heart scores. Key information such as lot number, sex, and harvest were provided for all cattle utilized in the analysis. Age was determined based on the difference between harvest date and birth date. Least squares means were obtained for traits of interest based on a series of linear models. The linear model equation is displayed below:

$$y_{ij} = B_0 + B_1x_{ij} + B_2x_{ij} + B_3x_{ij} + B_4x_i + e_{ij}$$

In the model above, y_{ij} represents the observed phenotypic values for the traits of interest. B_0 denotes the overall mean, B_1 represents the regression coefficient for the effect of heart score on y , where x_i corresponds to the i^{th} observation within the j^{th} harvest date, and B_2 represents the estimated effect of harvest date on y , with x_{ij} referring to the i^{th} observation within each harvest group. B_3 would represent the age of the individual in days for the j^{th} harvest date, and B_4 would represent the individual's sex.

Analysis of variance (ANOVA) was performed using the tidyverse and dplyr packages in R. The lsmeans package was used to estimate least-squares means for each phenotype, based on predictions from the fitted linear models. Phenotypic correlations among the traits were calculated using the GGally and Hmisc packages via the functions ggpairs, ggcorr (for heatmap visualization), and rcorr. Both Pearson and Spearman correlation coefficients were computed using Pearson's method, which assumes a linear association between traits, and Spearman's method, which assesses a monotonic relationship, meaning trait values increase and decrease together but not necessarily in a linear fashion. The Pearson correlation coefficients are calculated as follows:

$$r = \frac{\sum(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum(x_i - \bar{x})^2 \sum(y_i - \bar{y})^2}}$$

The equation for the Pearson correlation coefficient is presented above, and represented by r . Above, x_i represents the recorded phenotype for the i^{th} individual, and $\bar{x}$ represents the mean of the recorded observations for one phenotype across the sample. Similarly, y represents a different phenotype for the i^{th} individual and $\bar{y}$ was the sample mean for that phenotype. For example, x could be heart score phenotypes, and y would be hot carcass weight. Pearson correlations tend to capture linear relationships easily, with results ranging from -1 to 1 depending on the strength of

the relationship and in a positive or negative direction. Spearman correlations were calculated using the equation below:

$$\rho = 1 - \frac{6 \sum d_i^2}{n(n^2 - 1)}$$

Above, d_i represents the difference between the ranking of observations, n equals the number of observations, and ρ was Spearman's rank correlation. To achieve a ranking, the factors are arranged from highest to lowest; the number of rankings is determined by the number of observations, n . This type of correlation allows a bend in the fitted line, unlike Pearson correlations, which yield a straight line through the data points.

Results and Discussions

Phenotypic Differences

Summary statistics are listed in Table 3.2 below, with dairy and beef cattle sample sizes divided. The table included the number of observations, the mean, the standard deviation, and the range. Traits included in the summary statistics were those that could be biologically affected by cardiovascular distress. Initial summary statistics across breeds indicate overall differences, particularly in heart scores and hot carcass weights. The distribution of heart scores is shown in Figure 3.3 for both the beef and beef-on-dairy cattle. Phenotypically, beef cattle have, on average, higher heart scores with a greater amount of variation compared to their beef on dairy cattle counterparts. Dairy cattle had a mean heart score of 1.7 ± 0.65 , indicating that these animals, on average, tend to have lower or healthier heart scores than beef cattle, whose average heart score was 2 ± 0.79 . This difference in average HS indicates that beef cattle had a greater proportion with scores of 3 or higher, thereby raising the mean. In general, a similar pattern is observed for hot carcass weight, with beef cattle having heavier carcasses than dairy cattle.

Although these differences are based on summary statistics, it is evident that there may not be many differences; these results are expected given the type of cattle.

Table 3.2 Summary Statistics for phenotypic traits collected with heart score information. Right side displays beef cattle summary statistics and right side displays the beef-on-dairy summary statistics.

Trait	Beef Cattle					Beef x Dairy Cattle				
	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max
Heart Score	2,453	2.00	0.79	1.00	5.00	2,221	1.72	0.65	1.00	4.00
Backfat (mm)	2,434	17.53	5.34	4.06	41.71	2,159	16.26	4.83	2.03	54.86
Marbling Score	2,434	520.86	107.90	281.00	961.00	2,159	528.66	106.22	320.00	918.00
Ribeye Area(mm²)	2,434	14.22	1.53	8.32	19.56	2,159	14.35	1.48	9.58	19.30
Hot Carcass Weight (kgs)	2,102	399.29	47.90	213.76	560.68	2,183	388.38	38.77	220.50	523.07
Average Daily Gain (kg/day)	1,232	1.54	0.67	-1.57	4.43	-	-	-	-	-
Average Dry Matter Intake (kg/day)	730	10.71	1.47	4.94	15.65	-	-	-	-	-

In the dairy data, there were 859, 1148, 198, and 168 animals in the HS categories of Score 1, Score 2, Score 3, and Score 4, respectively. In the beef cattle data, the breakdown of HS

was 667, 1216, 476, 97, and 1 corresponding to scores 1, 2, 3, 4, and 5, respectively. The overall incidence rate for beef cattle was 23.4%, compared with 15.4% for dairy cattle.

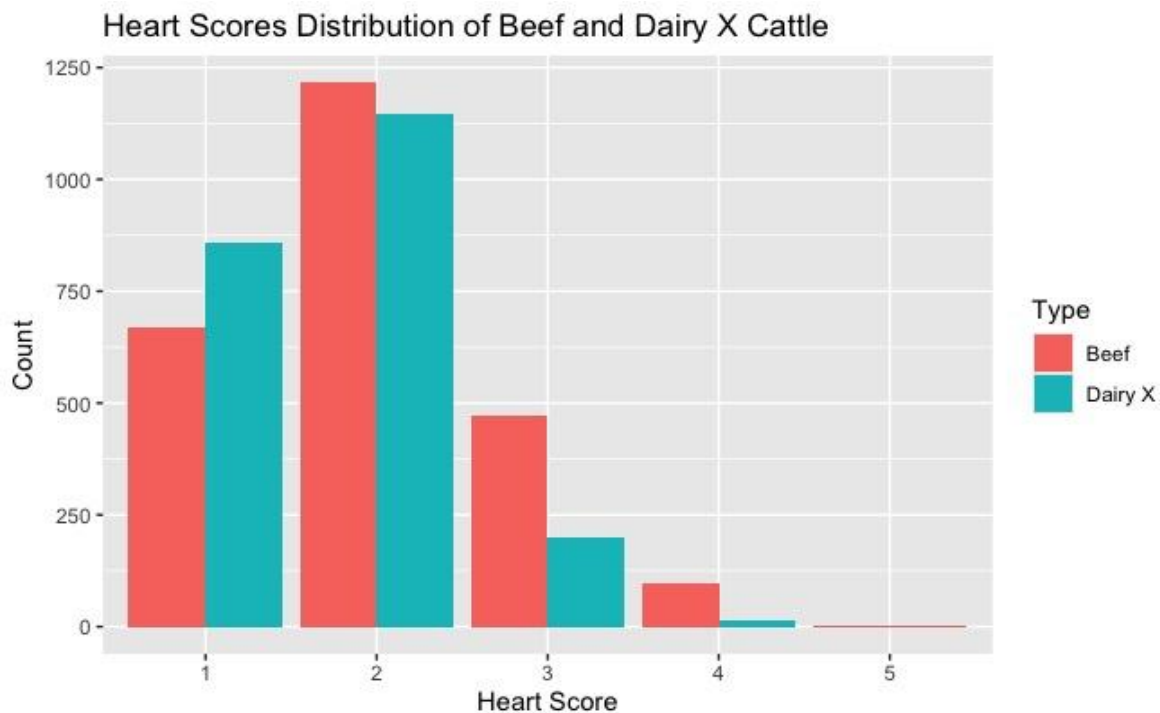


Figure 3.2: Distribution graph of counts of cattle per heart score for both breed populations side by side.

In these data, it was unlikely to observe cattle with a Score of 5 hearts at harvest due to its extreme risk for immediate heart failure. Buchanan et al. (2023) published a study that included a score of 5 in their evaluation due to the option to send cattle for early harvest if clinical signs were present. This contributed to the ability to capture these animals in the plant due to an earlier harvest date requested on an individual basis. This allowed those animals to be harvested properly rather than resulting in an early feedlot death. In this study, this option was unavailable; therefore, a lack of score 5 at harvest was present because these animals would have become early feedlot death cases. Death loss in the feedlot due to heart failure was unavailable in this study. The majority of our data resided in normal scores of 1 and 2 for both populations. It is to

be noted that the differences become more apparent as scores 3+ are more abundant in frequency in the beef population than the beef-on-dairy population.

Phenotypic Correlations

Initial analysis of phenotypic relationships was determined using Pearson and Spearman correlations. The phenotypic correlations are presented in Table 3.2 for the beef cattle and Table 3.5 for the phenotypic correlations of the beef-on-dairy cattle. Figure 3.3 showcases the fixed effect levels for the corresponding traits. Heat maps were constructed to visually present information and facilitate the identification of positive or negative relationships between traits and display Figure 3.4 and Figure 3.5. Directional relationships reveal traits that are phenotypically closely related, and any other potential linear relationships. In the beef population, heart scores had weak relationships with hot carcass weights (0.08), marbling (-0.11), average daily gain (0.15), and average dry matter intake (0.13), as shown in Table 3. Although these are weak, they are significant ($P < 0.05$). Spearman correlations reflected similar trends except for the inclusion of backfat measurements. If the relationship between two random variables is not linear, the Spearman correlation would be a better indicator of potential antagonism. These findings align with previous studies (Kukor et al. 2023), which reported the strongest significant relationships between hot carcass weight and marbling with heart score. The positive performance relationships observed in the feedlot further suggest that cattle exhibiting the most pronounced effects are typically those with great feeder intake and higher rates of gain. Overall, these results suggest that while heart scores exhibit statistically significant phenotypic relationships with several production traits in beef cattle, the magnitude of these phenotypic correlations is generally weak.

Table 3.3 Phenotypic correlations between phenotypic traits in beef cattle. Pearson correlations are represented in the green above the diagonal and spearman rank correlations are represented in the blue, below the diagonal. Significance is categorized as $P < 0.05$

Phenotypic Correlations: Beef Cattle							
	HS	HCW	BF	REA	MARB	ADG	ADMI
HS	1.00	0.08*	0.03	0.00	-0.11*	0.15*	0.13*
HCW	0.10***	1.00	0.40*	0.47*	0.18*	0.25*	0.63*
BF	0.06***	0.38***	1.00	-0.08*	0.31*	0.01	0.23*
REA	0.01	0.44***	-0.07***	1.00	-0.07	0.01	0.29*
MARB	-0.12***	0.17***	0.31***	-0.06***	1.00	-0.11*	0.15*
ADG	0.20***	0.30***	0.03	0.01	-0.12***	1.00	0.49*
ADMI	0.15***	0.59***	0.20***	0.27***	0.16***	0.50***	1.00
HS= Heart Score, HCW = Hot Carcass Weight, BF= Backfat, REA= Ribeye Area, MARB= Marbling, ADG =Average Daily Gain, ADMI = Average Dry Matter Intake							

Table 3.4 Solution Effects for traits based on linear models. The asterisk signifies significance ($P < 0.05$).

Effect	Heart Score	HCW	Marbling	Backfat	Ribeye Area
Sex (M)	0.0007	72.61*	-22.21 *	-0.05 *	0.11
Harvest Age	0.001	0.10	0.24	-0.0003 .	0.002 *
Heart Score	NA	Score 2: 23.23* Score 3: 28.00*	Score 3: - 12.52* Score 4: - 26.39*	Score 2: 0.02 *	Score 4: -0.32 *
Harvest Date	Varying Levels	Varying Levels	Varying Levels	Varying Levels	Varying Levels

HeatMap Phenotypic Correlations: Beef Cattle



Figure 3.3: Heat map to represent direction and strength of Pearson correlations in beef cattle.

In contrast, very few significant phenotypic correlations were observed in the beef-on-dairy population, as illustrated in Figure 3.3. Phenotypic correlations with heart score were nonsignificant and therefore not different than 0. This pattern may be attributed to the minimal data from cattle with higher heart scores (4+) in this dataset. In the beef-on-dairy cattle, however, correlations between other carcass traits were significant ($P < 0.05$) as expected. Feed performance was not analyzed in this dataset, and the inclusion of these traits in the future may aid in the exploration of potential phenotypic differences due to heart score.

Table 3.5 Phenotypic correlations between phenotypic traits for beef-on-dairy cattle. Pearson correlations are represented in the green above the diagonal and spearman rank correlations are represented in the blue, below the diagonal. Significance is ($P < 0.05$).

Phenotypic Correlations Beef on Dairy					
	HS	HCW	BF	REA	MARB
HS	1.00	0.03	0.04	0.01	0.00
HCW	0.03	1.00	0.42 ***	0.35 ***	0.15 ***
BF	0.04	0.41 ***	1.00	-0.04 ***	0.25 ***
REA	0.01	0.34 ***	-0.03***	1.00	-0.12 ***
MARB	0.00	0.14 ***	0.25***	-0.11 ***	1.00
HS= Heart Score, HCW = Hot Carcass Weight, BF= Backfat, REA=Ribeye Area, MARB= Marbling					

HeatMap Phenotypic Correlations: BeefXDairy



Figure 3.4: Heat map to represent direction and strength of Pearson correlations in beef-on-dairy cattle.

Furthermore, the severity of pulmonary hypertension may not follow a strict timeline for progression, as adverse effects may manifest only at later stages and at specific rates independently for individual cattle. Cardiovascular distress, such as increased pulmonary hypertension and effects of severe heart remodeling, does not show clinical signs until severe damage has already occurred. In Chapter 4, the strong positive genetic correlations between heart score and carcass traits indicate a more substantial underlying biological relationship. Although these relationships are not strongly expressed phenotypically, selection acts on genetics, not on raw phenotypic value. Therefore, cattle with a strong genetic value for carcass traits may be predisposed to increased cardiovascular remodeling, even if phenotypic signs of distress are not

observed. Over time, correlated responses could influence the likelihood that animals experience cardiovascular remodeling severe enough to reduce performance below predicted expectations.

The consistency of the phenotypic relationships between Pearson and Spearman supports the reliability of linear trends in heart scores, while the additional inclusion of backfat in the non-parametric analysis highlights that some relationships may follow nonlinear patterns. The analysis could be less linear as more moderate to severe heart scores are collected. Phenotypic correlations may fail to capture the relationship between scores 3 and 4+ due to the change in predicted pattern. Once a score of 3 continues to a score 4, cattle may begin to decline and experience a loss in desirable gains. Collectively, these findings emphasize the complexity of heart scores as a trait, reflecting both physiological and performance components, and suggest that further investigation with greater variations of sires and longitudinal data could better capture its phenotypic behavior across stages of growth and disease progression.

Using a linear model, all traits were fit separately as response variables, with heart score, harvest date, sex, and kill age as predictors. For the marbling score, the reference group of score 1 was 424.22, with heart score showing a significant relationship among the levels of heart scores ($P < 0.05$). The most notable effect was observed in animals with heart scores of 4 ($\beta = -26.39$, $P < 0.05$), indicating lower marbling scores in this group. Lot, sex, and age were also significant in the model, with steers having lower marbling scores than heifers. Hot carcass weights (intercept = 754.78) had a significant relationship with heart score 2 ($\beta = 23.23$, $P < 0.05$), and 3 ($\beta = 28.00$, $P < 0.05$), and steers were 32.66 kgs heavier when compared to heifers. Age was not found to be significant in the model. The lot was significant to the model, with varying lots having varying significant effects ($P < 0.05$) on the response variable. Harvest lot could account for season, location on the feedlot, specific group effects, management

differences, and overall is used to capture anything that would cause noise in the model due to cattle being raised at differing seasons. The intercept for backfat was 0.56, and a significant difference was observed for heart score 2 ($\beta = 0.02$, $P < 0.05$), while no other levels differed from the reference score of 1. Ribeye had an intercept of 12.45 in the model, and the only significant level for heart scores was score 4 ($\beta = -0.33$, $P < 0.05$). No levels of heart score were found to be significant for ADG. Average dry matter intake had heart scores 2 ($\beta = 0.91$, $P < 0.05$) and 3 ($\beta = 1.05$, $P < 0.05$), showing significance, while score 4 ($\beta = 0.88$, $P < 0.05$) showed a tendency toward the relationship. For the models evaluating the beef-on-dairy data, none of the evaluated traits showed a significant relationship with heart score. Even so, age and sex were found to be important predictors in the model.

Despite weaker phenotypic correlations, the least-squares means shown in Tables 3.5 and 3.6 are adjusted means derived from the linear mixed model. These means are adjusted for fixed effects rather than raw phenotypic means. The contemporary group for both beef and beef on dairy populations consisted of harvest date which encompassed both lot and time of year, while sex calculated potential sex effects in the data. Age was included in the model as a linear covariate because cattle varied in age and in the time they spent in the feedlot.

In the least-squares means, differences are more apparent after adjusting for other fixed effects such as sex, harvest age, heart score, and harvest date. Significance was determined based on p-values from pairwise comparisons, with heart score 1 as the reference. In beef progeny Table 3.5 When examining hot carcass weight, heart scores 3 and 4 had significantly different values than score 1 ($P < 0.01$). Hearts that graded 3 had the heaviest hot carcass weights, while hearts with a score of 4 had the lightest heart carcass weights. Similar findings were reported by Kukor et al. (2023), with the heaviest carcasses resulting from score 3 hearts, and the same

decrease was observed for score 4, suggesting that cattle may have lost weight during the feeding period due to cardiac stress. Thomas et al. (2018) reported a negative correlation between PAP and hot carcass weight, with cattle identified as high risk (>49 mmHg) weighing 33 lbs less than those cattle labeled as low to moderate risk (add the range in PAP). Heart score captures heart remodeling resulting from pulmonary hypertension, while PAP measures the pressure within the pulmonary artery, which helps diagnose pulmonary hypertension. Cattle in severe cardiac stress (heart score 4 and 5) due to pulmonary hypertension will lose weight and be the lightest cattle in the cohort, compared to those cattle that can maintain in themselves or were affected by pulmonary hypertension later in the trial have the heaviest carcass weights, perhaps due to increased weight affecting cardiac load. These cattle could be thought to also gain much slower but due to the progressive nature of the disease, since cattle have the highest weights in score 3, it is presumed that these cattle with later scores also achieve a similar pattern with their heaviest weights for the individual being around their score 3 timeframe and either drastically the heart changing or overtime as the heart shape changed weight gradually reduced. Marbling scores tended to decrease linearly, with score 1 having the highest marbling score and scores decreasing as heart scores increased. In terms of tissue deposition, intramuscular fat is the last to develop completely in finishing cattle. This is because muscle requires most of the energy. Once cattle reach slaughter weight and age, feed efficiency decreases, and fat deposition continues as energy is then redirected towards fat storage rather than muscle growth (Csapo and Kari, 2024). Cattle experiencing cardiac difficulties may disrupt this fat deposition as the cardiovascular system prioritizes nutrient exchange to vital organs and cellular processes. Ribeye areas from those individuals with a heart score of 4 were significantly smaller ($P < 0.05$), and no changes in backfat were present between scores. Feedlot performance in terms of average daily gain and

average dry matter intake was limited in this data with less than 1,200 head having dry matter intake data which included a smaller subsample size of beef cattle. Even so, cattle with a score of 3 ($P < 0.01$) had the highest dry matter intake of all the groups and the highest average daily gain, although this was not found to be significant ($P > 0.05$). These results indicate that cattle with higher HS typically have a higher genetic potential for growth traits. Individuals with a score of 3 are the heaviest and, as a result, consume more feed on average ($P < 0.05$). Overall, these results are consistent with those of Kukor et al. (2023), with worsening signs of pulmonary hypertension leading to lighter carcass weights, smaller ribeye areas, lower marbling scores, and decreased feedlot performance.

Table 3.6 Least Square Means table for beef progeny.

Least Square Means by Heart Score Category: Beef Cattle Group				
Trait	Heart Score			
	1	2	3	4
	LSM	LSM	LSM	LSM
Backfat(mm)	17.53 ± 0.25	18.03 ± 0.25	18.03 ± 0.25	17.02 ± 0.51
Marbling Score	542 ± 4.24	545 ± 3.64	532 ± 5.29	518 ± 10.70 *
Ribeye Area (mm²)	9161 ± 39	9226 ± 32	9226 ± 52	8968 ± 97
HCW(kgs)	392.81 ± 1.93	403.24 ± 1.66	405.51 ± 2.37 *	382.38 ± 43.00 *
ADG (kgs)	1.59 ± 0.03	1.63 ± 0.03	1.65 ± 0.04	1.48 ± 0.07
ADMI (kgs)	10.34 ± 0.22	10.75 ± 0.21 *	10.84 ± 0.23 *	10.75 ± 0.29 .

In Table 3.6, the beef on dairy cattle showed fewer phenotypic differences in the model. The largest effects, similar to those of beef cattle, would be hot carcass weight and marbling. Marbling tended to have a negative relationship with heart score, especially with heart score 4.

Hot carcass weights were different than what was previously seen; there were no differences in hot carcass weights, except in score 2, where carcass weights were significantly heavier than score 1. Visually, hot carcass weights appeared heavier for score 4; this difference was not significant due to the large standard error. Phenotypic differences in the beef on dairy progeny were much more difficult to visually detect than beef progeny in cardiovascular distress.

Table 3.7 Least Square means summary table for beef-on-dairy cattle.

Trait	Least Square Means by Heart Score Category: Dairy Cattle Group			
	1	2	3	4
	LSM	LSM	LSM	LSM
Backfat(mm)	16.00 ± 0.25	16.26 ± 0.25	16.51 ± 0.51	17.27 ± 1.27
Marbling Score	514 ± 6.36	514 ± 6.07	516 ± 8.71	493 ± 26.90
Ribeye Area (mm²)	9224 ± 58	9288 ± 52	9224 ± 77	9224 ± 232
HCW (kgs)	389.62 ± 2.33	393.25 ± 2.21 *	392.79 ± 3.20	399.61 ± 9.89

Conclusion

Results from this study indicate phenotypic differences between cattle with healthy and unhealthy heart scores. As cattle age and gain weight in the feedlot, those cattle that are predisposed to cardiovascular remodeling exhibit elevated cardiovascular stress in the feedlot as heavier weights are reached, which was reflected in the higher hot carcass weights in score 3 and the decreased carcass weights in score 4. Interestingly, while healthier cattle tend to have improved marbling scores, a highly desirable trait for consumers, carcass weight was lighter, and heart scores showed no cardiovascular changes in heart morphology. Heart scores of 3, which

represent the moderate stage of heart remodeling, do not appear severe enough to cause drastic differences in growth and carcass characteristics and are often favorable for weight. It is, however, not sustainable practice to aim for this heart score, as the progression of pulmonary hypertension is unpredictable, and the rate of progression is undetermined.

As shown, cattle with a score of 4 experience detrimental effects on hot carcass weight, marbling, ribeye area, average daily gain, and dry matter intake. A comprehensive study of feedlot performance would be beneficial for examining early-onset changes in these animals, helping to identify potential at-risk cattle, and, if possible, selecting cattle for early harvest. In beef-on-dairy cattle, these results are much more difficult to determine but could appear to be a rising concern in the future. As breeding strategies for beef-on-dairy cattle become more calculated, it is expected that these cattle will follow the pattern of the beef progeny as genetics improve their weight and growth, the feeding period will be shortened and intensified. It is advantageous to incorporate heart health into future sire selections to combat pulmonary hypertension, especially in source farms supplying the feedlots.

Overall, the results highlight potential trade-offs between cardiovascular health and the production performance in feedlot cattle. Although hot carcass weights may decrease slightly, the change could be minimal, and the gain in better marbling scores could compensate for improving carcass quality. Beyond the economic implications of early mortality, these findings are important for animal health and welfare. If the selection of lower heart scores can promote health and decrease incidence without substantially hindering genetic progress; it may offer a viable strategy for reducing the incidence of BCHF and improving long-term sustainability in affected operations.

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Chapter 4 : Heritability Estimates of Heart Score in Fattening Beef and Beef on Dairy Cattle

Introduction

Feedlot cattle can develop pulmonary hypertension (PH), a condition often called feedlot heart disease (FHD) or bovine congestive heart failure (BCHF), in low to moderate-elevation production systems. Although the exact causes remain unclear, cattle that experience severe pulmonary hypertension are at increased risk for early death, reduced performance, and additional health complications. Once pulmonary hypertension develops, it is irreversible, and its underlying factors in fattening cattle are not yet fully understood.

In high-altitude production systems, pulmonary hypertension, also known as high-altitude disease or brisket disease, is common due to the hypoxic environment (thin air). In these production systems, pulmonary arterial pressure (PAP) is used as an indicator of pulmonary hypertension, providing producers with a valuable tool for making informed breeding decisions. However, feedlot producers operating at lower elevations lack an equivalent indicator, and the connection between high altitude and feedlot heart disease remains poorly understood.

To address this knowledge gap, a heart-scoring system was developed as a phenotype to measure post-harvest heart health in feedlot cattle. In this study, 4,644 individual animals were fed, harvested, and had heart scores collected. These animals were sired by 224 bulls; heritability and genetic correlations between heart score and key carcass traits were estimated. The dataset included traits categorized into performance (Average Daily Gain, Average Dry Matter Intake), carcass (Marbling, Ribeye Area, Backfat, Hot Carcass Weight), and cardiovascular groups (Heart Score).

The objectives of this study were to:

1. Estimate the heritability of heart score using a multi-trait sire model for fattening beef cattle and beef-on-dairy cattle
2. Determine genetic correlations and covariances among phenotypic traits of interest and heart score.

Cattle raised at high altitudes, where elevations are greater than 1,500 m, commonly develop pulmonary hypertension, which worsens under persistent hypoxic conditions. As partial pressure of oxygen decreases with increasing altitude, the amount of oxygen available per breath declines, placing increased strain on the cardiopulmonary system. This condition, referred to as high altitude disease (**HAD**), has been described in literature since the early 1900's (**Glover, 1915**). More recently, however, cattle in feedlot environments at much lower elevations have exhibited similar clinical and pathological signs. This condition, termed Feedlot Heart Disease or Bovine Congestive Heart Failure, occurs in animals housed at altitudes below 1,500 m and is characterized by pulmonary hypertension and remodeling of the pulmonary artery and the right side of the heart, similar to HAD, but without the environmental hypoxia that triggers the cascade of events. This phenomenon is observed in humans with heart failure due to obesity and is paralleled in these fattening beef cattle (Krafsur et al. 2018). No effective treatment currently exists for either disease once heart morphology changes. In the case of HAD, affected cattle can be moved to lower elevations. In the case of FHD, the hypoxic trigger is unknown and unrelated to altitude. The physiological mechanisms driving pulmonary hypertension in low- to moderate-altitude environments remain unclear, suggesting that additional genetic or environmental factors may contribute.

To help mitigate high-altitude disease, the American Angus Association introduced a pulmonary arterial pressure expected progeny difference (PAP EPD, AAA, 2019) to assist

producers in selecting sires whose progeny are less susceptible to pulmonary hypertension. Pulmonary arterial pressure (PAP) is moderately heritable, with published estimates ranging from 0.24 to 0.34 (Crawford et al. 2016; Shirley et al., 2008). However, direct measures of PAP are invasive and are typically performed on replacement breeding animals around one year of age to assess susceptibility to HAD. Collecting sufficient PAP data on feedlot cattle is logistically challenging, and the relationship between PAP and right heart remodeling in feedlot populations remains unclear.

Currently, pulmonary arterial pressure (PAP) is used as an indicator of the degree of pulmonary hypertension (PH) in the animal, with higher PAP values reflecting greater PH severity and associated cardiac remodeling. However, PAP measurement requires specialized equipment and is not always feasible in commercial feedlot settings. As a complementary approach, a gross visual grading system developed at Colorado State University (Heffernan et al. 2020) has been implemented to characterize cardiac morphology at harvest. This heart scoring system provides a practical method for assessing structural changes associated with right-sided heart remodeling.

Variation in heart scores among individuals and between sires suggests that susceptibility to cardiac remodeling may have a genetic component. Supporting the biological relevance of this scoring system, a recent postmortem investigation of 346 feedlot mortalities by Long et al. (2023) evaluated the prevalence and characteristics of cardiac pathology. In this study, 30.6% of feedlot cattle mortalities exhibited cardiac enlargement or abnormal ventricular morphology in the absence of infectious disease. Objective measurements, including right ventricular size, heart width, and left ventricular wall thickness, were used alongside heart scores to assess the presence of congestive heart failure. Heart scores were strongly associated with estimated probabilities of

cardiac heart failure. Specifically, cattle with heart scores of 4+ had a predicted probability exceeding 0.90, while those with scores of 3 had a predicted probability of heart failure of 0.70. This probability declines sharply with scores 1 and 2, with values of 0.06 and 0.23, respectively (Long et al. 2025). These findings demonstrate a strong relationship between the subjective heart scoring and objective anatomical measurements, supporting the validity of heart scoring as a phenotypic indicator of cardiac remodeling.

Materials and Methods

All procedures were approved by the Colorado State University Institutional Animal Care and Use Committee (provide the number here). Two datasets were analyzed for each type of cattle: fattening beef cattle and beef-on-dairy cattle. The Angus-influenced beef cattle were raised and fed in a commercial feedlot in the Texas Panhandle at an elevation of 1,100 meters from 2020 to 2024. The beef-on-dairy cattle were raised in Southwest Kansas at an elevation of 850 meters from 2022 to 2024. Beef cattle were primarily Angus-influenced and included heifers (n= 1,215) and steers (n= 1,238). The beef-on-dairy data included heifers (n = 1,887) and steers (n = 304) with primarily Angus? Sires used to create these beef on dairy crosses?. Records lacking heart scores, contemporary group, or sire information were excluded. For both data sets, the following traits were recorded: heart score (HS), hot carcass weight (HCW; kg), ribeye area (REA; mm²), marbling (MARB), and backfat (BF; mm). Specific to the beef dataset, phenotypes of pulmonary arterial pressure (PAP; mmHg), average daily gain (ADG; kg/d), and average daily dry matter intake (DMI; kg) were collected. Throughout the study, cattle were managed under consistent dietary and husbandry conditions. Given the commercial nature of the production systems, the pedigree only included sire information, as dam information was not recorded. In the beef dataset, there were 130 unique sires represented, and for the beef-on-dairy dataset, there

were 94 unique sires represented. Summary statistics for all traits collected across both data sets are presented in Table 3.2 in the previous chapter.

Genetic analyses were conducted using the Animal Breeder's Toolkit (Golden et al., 1995) and the statistical software package ASReml (Gilmour et al., 2009). The model included harvest date, sex, and age at harvest(days). Data was primarily collected between 2021 and 2024, with most harvests occurring in the fall and winter months (October through March). Sex effects included steers and heifers with a single sex represented within a unique lot. Harvest age ranged from 398 days of age to 676 days of age in the beef-on-dairy sample and from 423 days of age to 655 days of age in beef. There were 28 harvest dates represented across 58 unique lots. A multiple-trait sire model was implemented using Best Linear Unbiased Prediction (BLUP) and is represented using matrix notation below:

$$\begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \\ y_6 \end{bmatrix} = \begin{bmatrix} X_1 & 0 & 0 & 0 & 0 & 0 \\ & X_2 & 0 & 0 & 0 & 0 \\ & & X_3 & 0 & 0 & 0 \\ & & & X_4 & 0 & 0 \\ & & & & X_5 & 0 \\ & & & & & X_6 \end{bmatrix} \begin{bmatrix} b_1 \\ b_2 \\ b_3 \\ b_4 \\ b_5 \\ b_6 \end{bmatrix} + \begin{bmatrix} Z_{a_1} & 0 & 0 & 0 & 0 & 0 \\ & Z_{a_2} & 0 & 0 & 0 & 0 \\ & & Z_{a_3} & 0 & 0 & 0 \\ & & & Z_{a_4} & 0 & 0 \\ & & & & Z_{a_5} & 0 \\ & & & & & Z_{a_6} \end{bmatrix} \begin{bmatrix} u_{a_1} \\ u_{a_2} \\ u_{a_3} \\ u_{a_4} \\ u_{a_5} \\ u_{a_6} \end{bmatrix} + \begin{bmatrix} e_1 \\ e_2 \\ e_3 \\ e_4 \\ e_5 \\ e_6 \end{bmatrix}$$

Where $\mathbf{y}$ was the vector of observed phenotypes, $\mathbf{b}$ was a vector of unknown fixed effects solutions, $\mathbf{a}$ was a vector of additive genetic effects, $\mathbf{X}$ and $\mathbf{Z}$ were incidence matrices relating observations in $\mathbf{y}$ to fixed effects in $\mathbf{b}$ and random effects in $\mathbf{a}$, respectively. Above, $\mathbf{e}$ was a vector of random residuals specific to individuals with observations.

In this model, random effects were assumed to have a mean 0 and variances as follows:

Genetic covariances

$$\text{VAR} \begin{bmatrix} u_{a1} \\ u_{a2} \\ u_{a3} \\ u_{a4} \\ u_{a5} \\ u_{a6} \end{bmatrix} = \begin{bmatrix} \sigma_{a1} & \sigma_{a1a2} & \sigma_{a1a3} & \sigma_{a1a4} & \sigma_{a1a5} & \sigma_{a1a6} \\ & \sigma_{a2} & \sigma_{a2a3} & \sigma_{a2a4} & \sigma_{a2a5} & \sigma_{a2a6} \\ & & \sigma_{a3} & \sigma_{a3a4} & \sigma_{a3a5} & \sigma_{a3a6} \\ & & & \sigma_{a4} & \sigma_{a4a5} & \sigma_{a4a6} \\ & & & & \sigma_{a5} & \sigma_{a5a6} \\ & & & & & \sigma_{a6} \end{bmatrix} \otimes A$$

Residual Covariances

$$\text{VAR} \begin{bmatrix} e_1 \\ e_2 \\ e_3 \\ e_4 \\ e_5 \\ e_6 \end{bmatrix} = \begin{bmatrix} \sigma_{e1} & \sigma_{e1e2} & \sigma_{e1e3} & \sigma_{e1e4} & \sigma_{e1e5} & \sigma_{e1e6} \\ & \sigma_{e2} & \sigma_{e2e3} & \sigma_{e2e4} & \sigma_{e2e5} & \sigma_{e2e6} \\ & & \sigma_{e3} & \sigma_{e3e4} & \sigma_{e3e5} & \sigma_{e3e6} \\ & & & \sigma_{e4} & \sigma_{e4e5} & \sigma_{e4e6} \\ & & & & \sigma_{e5} & \sigma_{e5e6} \\ & & & & & \sigma_{e6} \end{bmatrix} \otimes I$$

Figure 4.1: Kukor et al. 2023 Genetic and Residual covariances.

Above, **A** represented Wright's numerator relationship matrix, which defines the genetic relationships among individuals, and **I** was an identity matrix whose order was equal to the number of observations in **y**. The symbol σ_{ai} was the additive genetic variance for the i^{th} trait, and σ_{aij} was the additive genetic covariance between the i^{th} and j^{th} trait. The parameter σ_{ei} represented the residual variance of the i^{th} trait, and σ_{eij} was the residual covariance of i^{th} and j^{th} trait. The Kronecker product operator was denoted by $\otimes$. Heritability for each trait was calculated as the ratio of genetic variance to total phenotypic variance, where phenotypic variance was defined as

the sum of additive genetic variance and residual variance. Genetic and residual correlations are computed according to the following general equation

$$\frac{COV(a_{ij})}{\sqrt{VAR(a_i) \times VAR(a_j)}}$$

This equation can also be used for phenotypic or residual correlations.

Results and Discussion

Heritability

Genetic correlations and heritability estimate between heart score and carcass traits for beef and beef-on-dairy cattle are presented in Tables 4.2 and 4.3, respectively. In this study, the heritability of HS was 0.23 ± 0.05 for beef cattle and 0.06 ± 0.04 for beef-on-dairy cattle. Previous studies on a smaller subset of beef cattle reported a value of 0.27 ± 0.10 (Kukor et al. 2023). The highest recorded HS heritability in commercial beef production was 0.356, reported in the Pacific Northwest using a binary model in which scores 1 and 2 were assigned 0 and scores 4 and 5 were assigned 1. Researchers in this study wanted to determine the difference between severe remodeling and normal scores. Their design allowed for the capture of cattle with scores of 5 by enabling earlier harvest. Researchers concluded that the moderate, positive relationships observed in growth and feed intake traits suggest that selection for increased performance may inadvertently contribute to the rising prevalence of congestive heart failure in cattle (Buchanan et al. 2023). In our study, we were unable to capture scores of 5 because these cattle would have experienced early feedlot death and would not have reached the scheduled harvest dates. Furthermore, scores of 3 are included in our study because it is important to capture any negative consequences of cardiovascular remodeling, even in cases of moderate remodeling. Despite a lower heritability in our study, a similar conclusion can be formed from

previous heart failure findings, in which large, heavy cattle will be the most at risk due to cardiovascular strain. Given the moderate heritability estimates from beef cattle, genetic improvement is achievable, and selecting bulls with lower scores would decrease unfavorable genetic predispositions to cardiovascular remodeling. In the beef-on-dairy cattle dataset, heritability was estimated to be lower than that of the beef progeny cohort groups. This could be due to the dataset's lack of variability, as there were fewer moderate-to-severe heart scores because the present study was conducted in cattle that survived to harvest. The potential survivorship bias may partially explain differences in heritability estimates observed between the beef and beef-on-dairy cattle. Previous work has demonstrated breed-related differences in the timing and expression of FHD. Johnson et al. (2023) reported that cattle breed was significantly associated with the timing of heart failure, with beef-on-dairy progeny dying 37 days earlier than beef. These findings suggest that beef-on-dairy cattle may experience earlier onset or rapid progression through heart stages once remodeling begins. Therefore, differential survival by breed type provides a plausible biological explanation of the lower heritability estimate. Beef on dairy cattle also have a lower incidence rate suggesting although less common, the sensitivity to the cardiovascular changes could be affecting this population or contain a higher amount of super responders within a smaller subset. Beef cattle, however, have a significant number of moderate-to-severe scores, which increases phenotypic variation and can detect underlying differences. Additionally, the extended feeding period (beef versus beef-on-dairy) may result in slower rates of gain, as seen in traditional growth.

Genetic and Residual Correlations Beef Cattle

Genetic correlations reflect the extent to which pleiotropy influences two traits. A positive genetic correlation indicates that the genetic influences increasing one trait, in this case heart score, will also increase the other. A negative correlation suggests that improving one trait will genetically reduce the other. In heart remodeling, genetic correlations help predict how selection to reduce heart remodeling could affect other economically or biologically relevant traits. Larger magnitude correlations indicate greater shared additive genetic control between traits. This is helpful for traits that are closely related, such as carcass traits, where improving hot carcass weight would increase ribeye area. Understanding these genetic relationships is crucial because selection rarely affects traits in isolation. If selection is applied to reduce heart failure incidence, correlated responses in other traits will occur, depending on the magnitude and direction of their genetic relationships. This aids in potential trade-offs to help guide balanced breeding strategies that improve heart health without negatively impacting overall productivity. The results of the beef cattle heritability estimates are presented in Table 4.1

Table 4.1: Heritability estimates across diagonal, genetic correlations for traits above the diagonal, and residual correlations below the diagonal. Estimate and standard error included for each estimate.

Genetic Correlations and Residual Correlations for Beef Cattle								
Trait	Heart Score	REA	Marbling	Backfat	HCW	PAP	ADG	ADMI
Heart Score	0.23 ± 0.05	0.27 ± 0.19	-0.11 ± 0.19	0.22 ± 0.20	0.70 ±0.13	0.93	0.15 ± 0.24	0.36 ± 0.20
REA	-0.01 ± 0.02	0.37 ± 0.05	-0.05 ± 0.16	0.07 ± 0.18	0.65 ± 0.10	-	-	-
Marbling Score	-0.08 ± 0.02	0.03 ± 0.02	0.38 ± 0.06	0.35 ± 0.16	0.24 ± 0.15	-	-	-
BF	0.00 ± 0.02	0.00 ± 0.02	0.33 ± 0.01	0.29 ± 0.06	0.40 ± 0.14	-	-	-
HCW	0.02 ± 0.02	0.43 ± 0.2	0.25 ± 0.02	0.49 ± 0.02	0.48 ± 0.05	-	-0.09 ± 0.11	0.56 ± 0.12
ADG	-	-	-	-	-	-	0.31 ± 0.07	0.75 ± 0.12
ADMI	-	-	-	-	-	-	-	0.55 ± 0.07
Heart score, Ribeye Area (REA), Marbling, Backfat, Hot Carcass Weight (HCW), Pulmonary arterial pressure (PAP), Average Daily Gain (ADG), and Average Dry Matter Intake (ADMI).								

In beef progeny, the strongest correlation estimated in this study was between heart score and hot carcass weight, with a correlation of 0.70 ± 0.13 . These results support the hypothesis that increased carcass size may be associated with a greater genetic predisposition to cardiovascular remodeling. Buchanan et al. (2023), who used a binary model, report genetic correlations between heart scores that support trends similar to those found in this paper. Buchanan reported the genetic relationships between heart score and performance or carcass traits to be 0.46 (HCW), 0.08 (REA), -0.11 (Marb), -0.12 (BF), 0.29 (ADG), and 0.31 (ADMI). This relationship suggests that selection for larger carcass endpoints could indirectly increase cardiac structural adaptation by elevating metabolic demand and hemodynamic load. In contrast,

production traits such as average daily gain (0.15 ± 0.24) exhibited weak positive genetic associations with heart remodeling phenotypes. Although the magnitude of this correlation is small, this may indicate a modest shared genetic basis between accelerated growth and cardiac structural changes. The stronger relationship with hot carcass weight suggests that cardiovascular susceptibility may be more closely related to terminal size than to rate of gain. Although these two traits are closely related, growing animals of the same age or body weight may have different body compositions and compositions of gain, despite looking outwardly similar (Smith, 2007). This pattern may indicate that not all cattle are equally sensitive to rapid growth, but quickly achieving endpoint size could play a more substantial role in remodeling risks.

Correlations between heart score and the carcass traits ribeye area and backfat were 0.27 ± 0.19 and 0.22 ± 0.20 , respectively. These were similar to those reported in earlier studies by Kukor et al (2023) in subsets of the same dataset. In 2023, correlations between HS and carcass traits were 0.63 ± 0.20 (HCW), 0.13 ± 0.24 (BF), and 0.25 ± 0.22 (REA) (Kukor et al., 2022). In comparison with previously reported estimates, the genetic correlations between heart remodeling and both backfat thickness and ribeye area remained relatively stable. However, the genetic correlation between hot carcass weight and heart remodeling increased in magnitude, indicating a stronger shared genetic association in the updated analysis.

As additional data are collected, especially on animals with moderate to severe remodeling, the phenotypic differences could become more prominent, as severely remodeled cattle typically experience early feedlot death, the data on feedlot heart disease often misses the severe ramifications of cardiovascular remodeling. In general, these differences are captured as a gradual negative effect, but the rate of response is difficult to capture on an individualistic basis. The idea of larger animals being afflicted by various health conditions is not new. In the 1990s,

double-muscled cattle were reported to exhibit reduced cardiovascular fitness as muscling increased (Amory et al., 1992), suggesting that extreme selection for muscle development may impose physiological constraints on cardiac function. Although the present population does not represent a double-modeled phenotype, this historical evidence provides a biological context for the positive genetic associations observed between cardiovascular remodeling and carcass traits in the current study. Additionally, Angus cattle have been reported to exhibit moderate-to-high heritability estimates for carcass weight compared with other breeds (Kause et al., 2014). The predominance of Angus-influenced cattle in the study population may explain the observed relationship between heart score and hot carcass weight, as selection for growth traits in this breed is often accompanied by increased carcass weights. Consequently, selection pressure for increased carcass mass in Angus-based systems could result in more pronounced correlated responses in heart score.

Heritability estimates and genetic correlations for the beef-on-dairy population are presented in Table 4.2. Statistical significance of genetic correlations was assessed using approximate Z-tests (r_g / SE), with estimates considered significantly different from zero at $|Z| \geq 1.96$ ($\alpha < 0.05$). Under this criterion, marbling and heart score exhibited a significant negative genetic correlation (-0.67 ± 0.32), as the corresponding 95% confidence interval did not include 0, further collection of moderate to severe heart scores to increase the variability available in the beef on dairy data. Other correlations did not differ significantly from zero based on their standard errors. Heritability estimates for carcass traits in the present study were generally consistent with previously published estimates in beef-on-dairy populations, where carcass weight, ribeye area, and marbling are typically reported as moderately heritable traits. In this study, ribeye area, marbling, backfat, and hot carcass weight had significantly moderate

estimates at 0.37 ± 0.08 , 0.44 ± 0.08 , 0.22 ± 0.07 , and 0.38 ± 0.08 , respectively. Moderate heritability estimates for carcass traits are well documented in beef cattle populations (e.g., carcass weight, ribeye area, and marbling with mean estimates near 0.36-0.40 (Rio-Ultera and Van Vleck, 2024). While direct beef-on-dairy heritability estimates are less common, recent work in beef-on- dairy crossbreds focusing on genetic correlations and accuracy of EBV's confirms that carcass traits in beef-on- dairy crosses do exhibit sufficient additive genetic variation (Keele et al. 2024).

Table 4.2 Heritability estimates across the diagonal and genetic correlations for traits above the diagonal. Estimate and standard errors are included for each estimate.

Genetic Correlations for Beef on Dairy Cattle

Trait	Heart Score	REA	Marbling	Backfat	HCW
Heart Score	0.06 ± 0.04	0.40 ± 0.37	-0.67 ± 0.32	-0.04 ± 0.37	-0.16 ± 0.37
REA (mm²)		0.37 ± 0.08	-0.34 ± 0.22	-0.24 ± 0.25	0.58 ± 0.18
Marbling			0.44 ± 0.08	-0.21 ± 0.27	0.10 ± 0.24
BF (mm)				0.22 ± 0.07	-0.28 ± 0.27
HCW (kgs)					0.38 ± 0.08
Traits included: Heart Score, Ribeye Area(REA), Marbling, Backfat, Hot Carcass Weight(HCW).					

Unlike the beef cattle dataset, the beef-on-dairy population did not exhibit a strong genetic relationship between heart score and hot carcass weight (-0.16 ± 0.37), suggesting little evidence of shared genetic control between growth and heart score. In contrast, marbling was moderately heritable (0.44 ± 0.08) and showed a significant negative genetic correlation with heart score (-0.67 ± 0.32). This relationship suggests that alleles influencing intramuscular fat deposition may also influence heart score in beef-on-dairy cattle, although due to the large standard error, this still warrants further investigation with a larger sample size of beef-on-dairy

cattle, with more data needed on moderate to severe animals. Therefore, differences observed in carcass relationships between datasets may reflect variation in fat partitioning rather than uniform increases in carcass size alone. The beef-on-dairy dataset comprised primarily heifers, which are known to exhibit greater fat deposition than steers and bulls due to differences in circulating testosterone concentrations (Reddy et al. 2015). Sex-related differences in body composition are typically evident by approximately one year of age, with heifers demonstrating increased adipose deposition relative to intact males. Steers demonstrated values between heifers and intact males. Therefore, carcass composition in this population may reflect both sex effects and underlying dairy breed influence, which is associated with distinct growth and fat deposition patterns compared to terminal beef.

Similarly, Buchanan et al. (2023) reported genetic correlations between heart scores (treated as a binary trait) and production traits in Angus influenced commercial fed cattle. In their study, heart scores exhibited positive and moderate correlations (0.289-0.46) between growth traits and feed intake, with heart scores (scores 1 and 2), and were negatively correlated with performance and growth traits, whereas negative genetic correlations were observed with backfat and marbling (-0.12- 0.108). In the present beef-on-dairy population, the patterns are more variable. Heart score is positively correlated with ribeye area and negatively correlated with hot carcass weight and backfat. As stated previously, marbling score had the strongest negative correlation, suggesting that in crossbred progeny, intramuscular fat deposition may have a larger influence on heart remodeling risk than overall size. These comparisons indicate that while genetic relationships between growth and heart score exist in both groups, breed compositions due to crossbreeding may influence the magnitude and direction of correlated responses.

Beef-on-dairy cattle may still be predisposed to the development of right-sided heart failure, but the prevalence is lower than that of beef progeny. The continued use of genetically superior sires for growth and carcass traits, specifically with sires aimed for beef-on-dairy crosses, future crosses may exhibit similar results as their beef counterparts when looking at risk of cardiovascular remodeling. As seen from the beef subset, marbling has a lower genetic correlation with heart score and a higher genetic correlation with hot carcass weights. The opposite is shown in the beef-on-dairy cattle, most likely due to the heterosis effect of the crossbred. Previously, beef bull semen was used on dairy cows. Now there is further evidence that choosing the right bull matters even for the beef-on-dairy terminal cross. Targeted terminal sire selection programs in beef-on-dairy systems further emphasize the importance of understanding correlated cardiovascular risk. Beef-on-dairy cattle would be the most profitable if they became more uniform with beef cattle, hence emphasis on larger hot carcass weights in a quicker feeding period.

Conclusion

These findings indicate that cardiovascular remodeling has a multifactorial genetic basis, with distinct contributing traits indifferent populations. In beef cattle, the genetic influence of overall carcass size is prominent, while in beef-on-dairy cattle, variation in marbling shows the strongest association with heart score. This dual perspective highlights two complementary pathways through which selection for growth and carcass traits may impact cardiovascular health. Feedlot heart failure is observed in moderate to low altitude populations, demonstrating that environmental stressors alone do not explain the disease (Buchanan et al. 2023, Kukor et al. 2021, Neary et al 2016). Moreover, intensive selection for rapid growth and carcass performance may increase the biological risk of heart remodeling in genetically susceptible individuals,

highlighting the importance of balanced selection strategies that consider both productivity and the physiological limits of the cattle's genetic potential.

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Chapter 5 : Genome-Wide Association Study Using JWAS in Julia Programming

Introduction

Genomic selection has become a central component of modern beef cattle breeding programs. Advances in high-density single nucleotide polymorphism (**SNP**) genotyping platforms now enable producers to submit tissue samples and receive genomic predictions that estimate the genetic merit of economically relevant traits. Genetic samples can be collected as early as embryonic development, but are more commonly taken from live calves, allowing breeders to know the genetic potential of each animal prior to growth stages. These genomic predictions enhance the accuracy of estimated breeding values (EBVs), particularly for those young animals that lack phenotypic records. Overall, the adaptation of this technology has accelerated genetic progress and improved the selection of traits related to productivity, health, and disease resistance. The integration of genomic information into breeding programs has enabled producers to make earlier and more informed decisions in herd management, ultimately improving overall performance and reducing the prevalence of undesirable traits.

The theoretical foundations of marker-assisted selection were established by Fernando and Grossman (1989), who extended best linear unbiased predictions (BLUP) methodology to incorporate genetic marker information within mixed linear models. Their framework allowed markers linked to quantitative trait loci (QTL) to contribute to the additive genetic effects estimated within the model while also enabling prediction for individuals with limited marker information through pedigree relationships. This advancement provided a critical bridge between classical quantitative genetics and molecular genetics, laying the groundwork for today's genetic technologies.

Although marker-assisted selection allowed breeders to use marker information to enhance EBVs, its effectiveness was limited, and further development of using this information as a visual tool to map QTL associations became more useful for connecting genetic effects to biological reasoning. The development of genome-wide association studies (GWAS) provided a powerful statistical framework for identifying genomic regions associated with complex traits. GWAS evaluated thousands of SNP markers across the genome to detect statistical associations between genetic variants and phenotypic differences. Many economically relevant traits are polygenic, meaning that multiple loci influence the trait with small effects. When combined, all these loci will contribute a much larger effect, but varying combinations could increase or decrease an individual's genetic potential. GWAS plays an important role in revealing the underlying genetic connections of these traits, as well as of more complex traits such as health, stress, or reproduction. Identifying these regions can improve the overall biological understanding of why these differences occur and to what extent they will influence the phenotypes being explored.

Feedlot heart disease presents a unique challenge for genomic evaluation. The trait is physiologically complex and has been reported to exhibit low to moderate heritability in previous studies (Kukor et al., Buchanan et al., Johnson et al). Traits influenced by multiple biological systems and environmental factors often follow polygenic inheritance patterns, making them difficult to manage and select on phenotypic information alone. Additionally, heart failure is not observable until post-harvest, which limits the ability to detect or treat live animals at risk of developing the condition. The addition of genomic selection could positively impact disease prevalence while highlighting biological causes.

Previous studies on heart score that have contributed to GWAS in feedlot heart failure

have shown mixed results. Heaton et al (2022) identified three genes associated with susceptibility to the condition. These identified traits led to the development of a genetic test to identify cattle with improved heart health, available to producers. This discovery contrasted with previous pulmonary arterial pressure studies, another method for measuring heart health in live cattle, which showed a polygenic effect across the genome in yearling PAP (Zeng et al. 2023). Furthermore, Johnson et al. reported heart score as a binary trait, in their GWAS there was evidence that multiple areas contributed small amounts of variance to heart score. The results showed multiple smaller peaks across the genome, but no peaks were past a significant threshold of larger genomic proportions. These contrasting findings highlight the need for additional investigation to better characterize the genetic basis of heart score in feedlot cattle. The objective of this study was to conduct a genome-wide association analysis using genotyped cattle with heart score phenotypes to identify genomic regions associated with variation in the trait. Identifying candidate loci and genomic regions may improve the understanding and lead to the improvement of the biological mechanisms underlying cardiovascular remodeling in feedlot cattle.

Material and Methods

Raw genotype data were obtained from a commercial bovine 60k custom SNP panel for all available, sampled cattle within the study population, including sires and grandsires. Phenotypic records associated with heart score, contemporary group classifications (lot and sex), and additional covariates were extracted and subjected to quality control procedures prior to analysis. In this study this would include cattle with heart scores, known sire information, and proper contemporary group classification. Data cleaning involved removing duplicate or

incomplete records and aligning animals in the phenotype file with those in the pedigree and genotype files.

Genotype data consisted of 67,732 single nucleotide polymorphism (SNP) markers distributed across the bovine genome. SNP marker identification and genomic positions were standardized using a reference ARS-UCD1.2. SNP map to ensure the marker names corresponded correctly to their physical base pair locations on the bovine genome, to accurately map these locations to the correct genomic windows. The pedigree contained 210 unique sires and 4,909 individuals overall. Of the 4,909 individuals with data, 3,789 possessed valid genotypes. Dam information was not available. Despite incomplete parental information, the pedigree still provided a useful relationship structure for modeling. Progeny who had no sire information were dropped from the evaluation. Ensuring pedigree completeness is critical for model convergence.

Recent developments in single-step genomic prediction methodologies have further advanced the ability to incorporate multiple sources of information in genetic evaluations. Single-step genomic best linear unbiased prediction (ssGLUP) models integrate pedigree, phenotypic, and genomic marker information into a unified analysis. This approach allows all available animals to contribute to the genetic evaluation. The software platform, Julia-based Whole Genome Analysis Software (JWAS) (Habier et al. 2011, Fernando R. and Garrick D. 2013), implements Bayesian, mixed-model approaches to simultaneously estimate genomic breeding values and identify genomic regions that contribute to trait variation. These models can also be extended to perform genome-wide association analyses to estimate the proportion of genetic variance explained by the marker. JWAS was performed utilizing the method described by Fernando and Garrick (2018).

The Statistical Model

A single-step genomic mixed-model was used to evaluate the association between SNP markers and heart score phenotypes. Below is the general linear mixed model implemented for this analysis:

$$HS = \mu + cg + \alpha + g + e$$

Above, **HS** represented heart score phenotype, μ was the overall intercept, **CG** was the contemporary group (fixed effect of lot and sex), α represented the random additive genetic effect associated with individual animals, g was the vector of SNP marker effects, and e represented the residual error term. All genotyped and nongenotyped cattle receive a gEBV as a result of this model, which is one of the advantages of using this method.

SNP marker effects were estimated using the Bayes C method, a Bayesian variable selection method that is standard in Genome Wide Analysis studies (Habier et al., 2011). Bayes C is an extension of other Bayes methods, with the goal of identifying genomic regions associated with complex traits. This method assumes only a portion of markers across the genome contribute non-zero effects. This assumption reflects the biology that many complex traits are influenced by a small subset of loci with a combined measurable effect. BayesC does not assume SNPs have a known marker effect, unlike BayesA and BayesB, and instead allows this to be inferred by data.

A downstream SNP map was provided for these animals; there were 69,731 SNP markers across all genotyped animals. All genotyped animals had to be in the pedigree to converge correctly. The SNP map file was uploaded to examine base-pair positions and standardized to align properly with genotype marker names. The results of this model will produce a subset of markers in the genome that have a nonzero effect and exclude those with no additional variation.

The model assumes that each marker effect follows a normal distribution with some variation or excludes those with zero estimates. The analysis was then run using Markov Chain Monte Carlo (MCMC), with 60,000 iterations and a 15,000-burn-in. The model was run three times with 50,000, 60,000, and 75,000 iterations. Results from all three were correlated with each other to determine convergence. Results from this indicate that the run from 60,000 to 75,000 had a correlation of 1, models had a Pearson correlation greater than 0.98, indicating that they had converged appropriately, and marker solutions were unlikely to change with the number of rounds. MCMC is a computational algorithm used to approximate the posterior distribution of model parameters when direct solutions are not feasible by generating a sequence of samples that converge to the target posterior distribution over time. In Bayesian models, parameters such as marker effects represent unknown quantities within the statistical model. Rather than estimating a single value, Bayesian methods estimate a distribution over possible parameter values consistent with the observed data. During iteration, MCMC decides whether to include or not include a SNP. When an SNP is included, its effect is sampled from a normal distribution, and over multiple rounds, the model captures the pattern.

Following model convergence, marker effects were extracted from the posterior sample, and 1Mb genomic windows were used to calculate the Window Posterior Probability of Association (WPPA) and proportion of genetic variance for each region. Visualization graphs were produced to highlight peak regions using a Manhattan plot style of graph. In this dataset, 1,265 unique regions were identified with nonzero estimated genetic variance. The genetic variance plot showed the amount of genetic variance each marker contributed, and the WPPA reflects the probability that a genomic window truly contributes to trait variance. This is determined by MCMC, which estimates how often this SNP appears to explain some proportion

of the variance. In total, the MCMC is computationally demanding, and the number of iterations and burn-in is study-specific.

Genome-Wide Association Study

Posterior samples of SNP marker effects were extracted and incorporated into the genomic windows. SNP markers were grouped into 1 Mb windows across the genome. This window-based approach helps account for linkage disequilibrium among nearby markers and enables the identification of genomic regions that contribute to phenotypic variation. The three measurements collected were genetic variance, window posterior probability of association, and posterior probability of association for heart score. Genetic variance in this context refers to the amount of additive genetic variation the SNPs explain in the model. The Window Posterior Probability of Association is the probability that at least one SNP in the window contributes to trait variability, indicating that the region accounts for additive genetic variability in the trait. The Posterior Probability of Association for heart score is the probability that a single SNP has a non-zero effect. This would encompass the proportion of MCMC iterations where the SNP are included in the model. A SNP can result in having genetic variance, but the WPPA and PPA provide more confidence that this effect is significant to the model and helps indicate actual specific areas of interest and filter out nonzero but lowly appearing regions or SNP's as important to the trait.

Results And Discussion

The single-step JWAS successfully converged, and marker variance components, heritability estimate, estimated breeding values, and genetic variance were generated. The identified markers indicated a polygenic effect, with multiple peaks. In the data, 1,265 nonzero estimates were identified as contributing to nonzero genetic variation. Table 1 displays the top 20

SNP locations ranked by posterior probability association for each individual SNP. Figure 1 and Figure 2 show the Manhattan plots of these nonzero estimates. Previously, two independent genomic regions were identified in Heaton et al. (2024) which were associated with bovine congestive heart failure and used as a marker for the disease in a commercialized genetic test. These regions were associated with the arrestin domain containing protein 3 gene (ARRDC3) and the nuclear factor IA(NFIA). These two genes were found to increase the likelihood of BCHF if both risk alleles were present in either gene. The ARRDC3 was found in chromosome 7 and NFIA was found on chromosome 3. The top chromosomes in this study that show Locations on chromosome 9 have been found to be associated with calf mortality, beef marbling, and fertility. Regions on chromosome 20 have been implicated in milk production traits, carcass composition and quality, disease resistance (e.g., pinkeye, foot rot, and bovine respiratory disease), the slick coat gene, and the growth hormone receptor. Areas on chromosome 6 have a significant impact on milk production, such as milk yield, fat, and protein. Chromosome 6 also consistently maps to growth and body composition in beef cattle, coat colors, and calving ease. Although each area has interesting characteristics, genomic windows had to be closely examined to identify any known or previously known functionally relevant genes. Investigating annotated genes or known markers within these windows can provide some biological context and help identify candidate genes associated with this trait. Based on Figure 1, the mapping of the proportion of genetic variance peaks on Chromosomes 9, 3, and 20 each explains around 0.2% of the total genetic variance at that marker location. There is greater confidence that these locations are significant because of the posterior probability that they also have high spikes, or high confidence that these areas are relevant. Table 1 numerically shows the location, the amount of

genetic variance estimated, the posterior probability that the marker is associated with the window, and lastly the posterior probability that the marker is associated with the trait.

The following areas were identified, and, using the Bovine QTL mapping software, specific SNP regions were explored to assess their relevance. The top 20 windows are identified in Table 5.1. SNP windows displaying Manhattan plots of Window posterior probability associations and proportion of window genetic variance are displayed in Figure 5.1 and 5.2.

Table 5.1 Marker effects table for heart score in order of highest posterior probability association for heart score. Ranked: order of highest to lowest PPA_t. PrGenVar represents the proportion of genetic variance associated with each window, WPPA: window poster.

Ranked	Chromosome	Start_SNP	End_SNP	prGenVar	WPPA	PPA_t
1.	9	10139748	10975124	0.125	0.657	0.657
2.	3	32005812	32993597	0.113	0.571	0.614
3.	20	4053817	4999156	0.091	0.328	0.519
4.	6	36018028	36970336	0.089	0.312	0.467
5.	6	37000373	37999069	0.090	0.307	0.435
6.	6	38021694	38970621	0.086	0.296	0.411
7.	5	56007661	56957884	0.086	0.276	0.392
8.	7	3004323	3947888	0.066	0.149	0.362
9.	20	5000086	5982873	0.068	0.137	0.337
10.	3	33003020	33984136	0.067	0.115	0.315
11.	3	88002627	88991817	0.059	0.104	0.296
12.	6	87021332	87947782	0.057	0.101	0.279
13.	30	15049860	15999390	0.061	0.097	0.265
14.	10	29015173	29940937	0.054	0.092	0.253
15.	1	3033433	3998532	0.091	0.091	0.242
16.	7	90063596	90997484	0.056	0.091	0.233
17.	13	6038638	6940730	0.044	0.091	0.224
18.	14	3040885	3980151	0.060	0.089	0.217
19.	23	4023817	4983207	0.060	0.088	0.210
20.	7	2059143	2990881	0.058	0.085	0.204

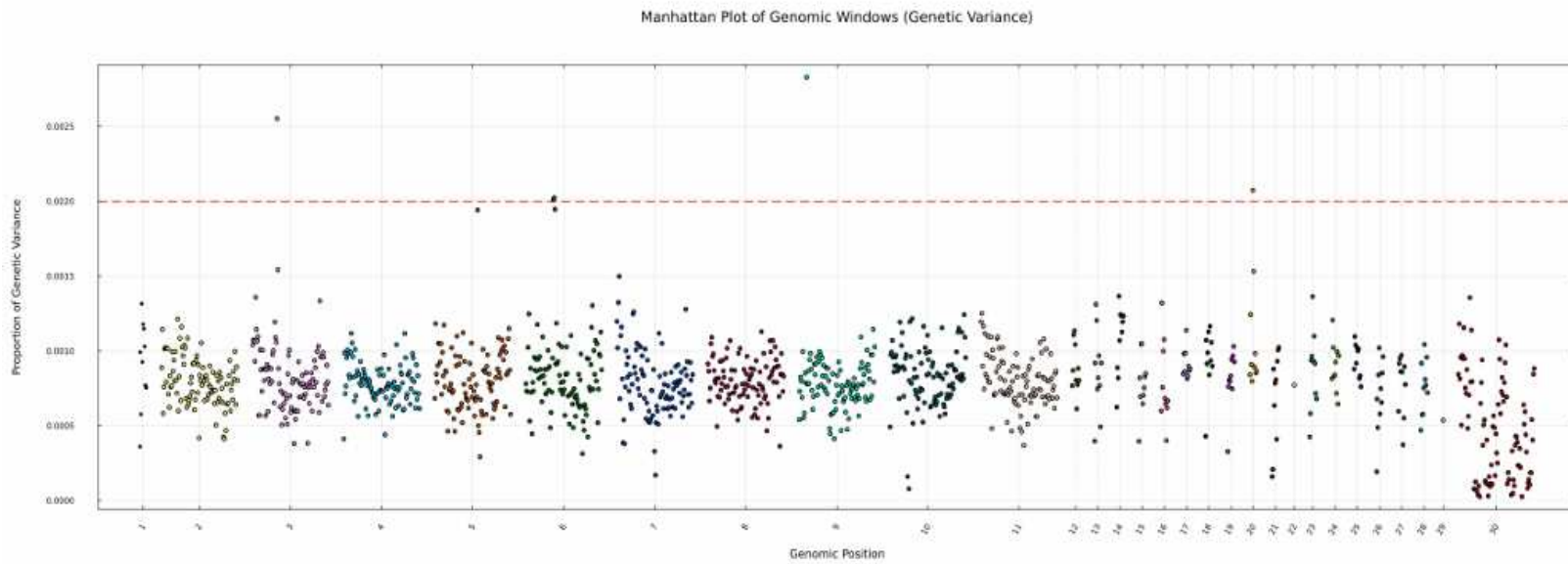


Figure 5.1 Genetic variance manhattan plot for nonzero estimates. Genetic variance proportions were calculated using genetic variance of the marker divided by the sum of total genetic variance across all windows. Red line indicates all proportions greater than 0.0002

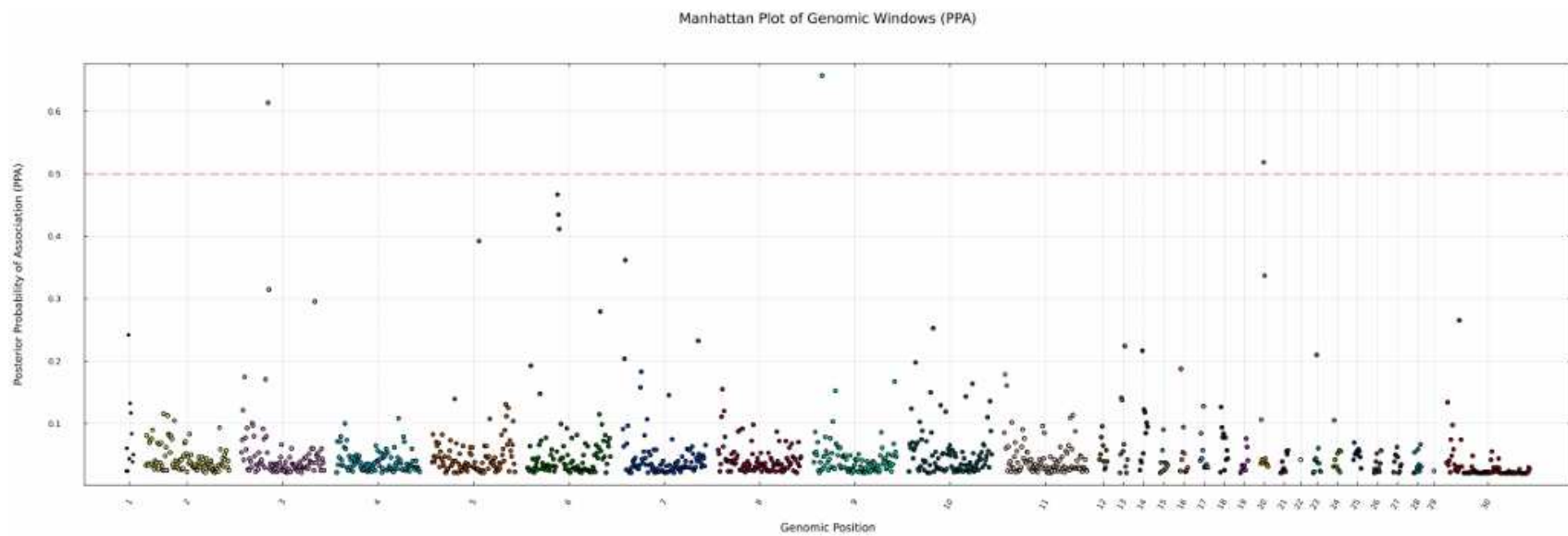


Figure 5.2 Manhattan plot for WPPA for non zero estimates, probability of 0.5 indicated by red line. Higher probability relates to the likelihood that the genetic variance explained by the window is relevant to the trait.

Chromosome 1

This region has not been previously commented on in heart score literature as a region of interest. Majority of the window regarding chromosome 1 in window 3033433- 3998532 were characterized by QTL's that explained foot ulcers, calving, horn presence, and, most relevantly, body weight. One study identified QTL 24745 as associated with body weight, specifically body mass, in their study of 18,274 head of cattle encompassing 10 beef cattle breeds, including Angus and Simmental. (Saatachi et al. 2024). This trait was identified specifically in the Simmental breed, which is partially represented among the breeds used in both beef and beef x dairy cattle in this study.

Chromosome 3

The areas indicated on this chromosome had several different types of associations and QTL present. The majority of QTL in Angus have been linked to shear force or connective tissue amount, which are related to meat tenderness (citation needed). In Brangus cattle, where animals were 5/8 Angus, body weight was associated with QTL 22756, with a positive association attributing to differences in body weight (Peters et al., 2012). In Holstein cattle, this area (QTL 178942) is associated with a tendency toward susceptibility to bovine tuberculosis in dairy cattle in Mexico (Gonzalez Ruiz et al., 2019). Other areas along chromosome 3 were also found to be associated with a tendency of relevance towards body weight in Angus and Simmental cattle, as explained by QTL 164245 (Akanno et al. 2018). The further spike at the end of chromosome 3 had several QTL identified in the Holstein breed, including QTL 36966, which is a significant marker ($P < 0.05$) for lean meat yield in a carcass trait and growth study aimed at Holstein cattle raised for beef (Doran et al. 2014). Chromosome 3 was also identified as a significant region in the Heaton et al. study on BCHF, although it did not appear in this study.

Chromosome 5

Chromosome 5's region encompassed a variety of milking traits in Holstein as well as several carcass traits. QTL 22850 was also found to be significant in the Brangus study, reported on chromosome 3, and explained differences in ribeye muscle area (Sunday et al. 2012). Body weight differences in Chinese Simmental cattle were associated with QTL 237639 (Du et al., 2021). In a study conducted in Brangus steers by Baeza et al (2011), this area showed a tendency association with the gene STAT6, which is a signal transducer and activator of transcription 6 interleukin-4 induced, which relates to carcass weight, specifically in this study.

Chromosome 6

The first significant area on this chromosome contains 1,189 known SNPs. One SNP related back to previous studies by Zhang et al. (2020) and Leal-Gutierrez et al. (2020) for average daily gain, metabolic weight, and marbling score in Angus cattle. Most of this area involved milk production traits in Holstein cattle. The next significant region contained 6,639 SNPs. This area had a large subset of bone weight-related SNPs. In a Canadian beef cattle study, Zhang et al. (2020) identified significant markers for average daily gain, dry matter intake, and metabolic body weight. Bone weight markers, such as those found in Niu et al.'s study (2021) in Chinese Simmental cattle, were found to be a significant marker for differences in bone weight in cattle. Wang et al. (2020) identified additional carcass-weight-significant markers in commercial beef cattle. The following region had 1,041 known QTLs and showed a pattern similar to the previous region, with research on bone density, metabolic rate, and average daily gain being the most prevalent traits studied in the area. The last area on chromosome 6 contained 8,419 records, and a large proportion of these were SNPs associated with ketosis, milk fever, and displaced abomasum.

Chromosome 7

The first region of chromosome 7 identified 31 SNPs associated with body height, marbling score, connective tissue amounts, milk yield, and other reproductive traits. Marbling score in Angus was identified in the same study by Leal-Gutierrez et al. (2020) as a highly significant factor in explaining marbling score differences. Body weight gain QTLs discovered in the study by Snelling et al. (2010) were also found in this area. Repeated studies in carcass traits in beef cattle across the significant window in Table 5.1 showcases a strong potential association with heart score and carcass traits. Previously, Gonzalez-Ruiz also showed an association on chromosome 3 with bovine tuberculosis susceptibility, which is again found on chromosome 7 at QTL 178906. The next region of chromosome 7, corresponding to number 16 in Table 1, had 0 known SNPs associated at this location. The last location on chromosome 7 was found to have 40 SNPs associated with marbling score QTL 231819 and QTL 231827, as reported by Leal-Gutierrez et al. (2020) in Angus cattle. The window 90063596 to 90997484 associated with QTL 109627006 located on chromosome 7:90458755-90997484. This same QTL was reported to be related to average daily gain and lean muscle yield in Brangus cattle (Peters et al. 2012). Interestingly, this same QTL was reported in a Genotype identification study in Angus heifers when analyzing pulmonary arterial pressure. This area was an associated SNP related to adjusted birth weight of the cattle and found to be significant to yearling PAP measurements (Cockrum et al. 2019). This positive known QTL association between both studies showcases the genetic evidence for the link between pulmonary arterial pressure and heart score, furthermore this provides more evidence of how traits associated with cattle weight may be highly involved with cardiovascular outcomes.

Chromosome 9

This area was the highest contributor to genetic variation in these data. In this region, there are several associations with marbling scores in Angus cattle (Kolpakov et al. 2025). A QTL related to subcutaneous fat (QTL 223804) was also found in this region; however, this published QTL did not contain a research paper or reference source attached to determine bovine breed studied. Body weight in Angus cattle along with bone percentage studies, and longissimus muscle area are highly associated with the region for Angus, Holstein and Charolais. This is also the only region where immune markers for basophils and eosinophils were noted as blood metrics with known associations with the area (Chinchilla-Vargas et al., 2020). There were only 13 unique SNPs found in this location.

Chromosome 10

Chromosome 10 in our significant region indicated many traits related to reproduction in cattle, and QTL 7092 and QTL 10865, relating to Longissimus muscle area and subcutaneous fat percent in beef and dairy, were published in the database, but no reference source attached to the QTL to identify research source contributing to this finding. An association study by Snelling et al. (2010) presented QTL 68173 as significant ($P < 0.05$) in crossbred beef cattle weight differences.

Chromosome 13

The area on chromosome 13 has been associated with Holstein traits, with most research in this region focusing on dairy form, stature, udder ease, conformation, and foot and leg traits as depicted by the QTL Bovine Library within the significant windows discovered. Beef tenderness score in Angus cattle was mapped to QTL 228661 in this region to be a significant marker, as

well as QTL 234099 relating to connective tissue amount in Angus-sired progeny (Leal-Gutierrez et al. 2020).

Chromosome 14

In this region, 2,751 SNPs were identified, all of which were milk-related traits in Holstein, primarily encompassing milk fat percent, milk yield, and milk protein percentage. Due to the large number of QTLs associated with this study, dairy cattle with cardiovascular remodeling could offer potential explanations.

Chromosome 20

This chromosome had two significant regions. The first area showed known SNPs associated with QTL 234561, which were related to the previous study by Leal-Gutierrez (2020) on the amount of meat connective tissue in Angus-sired cattle. There was evidence of this the region peak in chromosome 20 being associated with carcass weight in Angus cattle (Baneh et al., 2025). Average daily gain associations in Canadian beef cattle were found in QTL 186241 (Zhang et al 2020). Overall, a large number of carcass weight and body weight QTLs reside in this area with several known SNP markers and QTL regions attached.

Chromosome 23

This region had several body weight and carcass-weight traits, but no known research sources were attached. There were 55 QTLs identified in this area relating to reproduction and body characteristics in Angus and Holstein.

Chromosome 30

This chromosome had no matches to known QTLs associated with any SNPs in the area. In summary, there is evidence of a strong association between heart score and body weight, marbling score, bone weight, carcass weight, fat, and muscle size. These associations strengthen the idea that biologically, these cattle could be associated with greater genetic potential for these

areas. According to the QTL database, there are currently no published markers associated with heart health, heart score, or cardiovascular health traits.

Conclusion

This study evaluated the genomic structure of heart score in feedlot cattle using genome-wide association analysis implemented through a single-step framework. Several chromosomal regions, particularly on 9, 2, 20, and 6, demonstrated notable signals. Although it previously appeared that few markers were responsible for the differences, this data shows the complexity of the trait. While no direct QTL for heart health has been identified currently, the overlap similarly on chromosome 7 displays a strong association with weight and cardiovascular health. This also yields promising results that as more data is collected in these traits These areas provide potential candidates for further development and investigation. Future research incorporating larger datasets, more unhealthy heart scores, and comparisons with pulmonary arterial pressure JWAS should be conducted to further understand the biological relationships.

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Chapter 6 : Conclusion

Feedlot heart disease has emerged as an important health trait and economic concern in modern beef production systems. Despite increasing reports of cardiovascular remodeling in feedlot cattle raised at moderate to low elevations, the mechanisms contributing to this condition remain poorly understood in literature. The objective of this research was to evaluate heart score as a phenotypic indicator of cardiovascular remodeling and to investigate its phenotypic relationships, genetic architecture, and genomic associations with economically relevant production traits in both beef and beef on dairy cattle populations.

Phenotypic analyses demonstrated measurable differences in carcass and performance traits across heart score categories. Cattle with moderate remodeling (score 3) tended to exhibit heavier carcass weights and increased feed intake, while individuals with severe remodeling (score 4) showed a decline in carcass weight, ribeye area, marbling score, and overall performance. These findings suggest that early stages of cardiovascular remodeling may occur without obvious production penalties, whereas more advanced stages can negatively affect both carcass characteristics and feedlot performance. Phenotypic correlations between heart score and production traits are generally weak, indicating that the biological relationship between cardiovascular remodeling and performance may not be readily detectable through the raw phenotypic data.

Genetic analyses revealed that heart scores possess a measurable genetic component, particularly in beef cattle, where heritability estimates indicated improvement through selection is possible. Genetic correlations further demonstrated positive relationships between heart score and carcass size traits. This suggests that terminal size may be genetically predisposed to

increased cardiovascular remodeling. In contrast beef-on-dairy cattle exhibit a lower heritability estimate and weaker relationship between growth traits. These differences mostly reflect the variation of scores collected, breed composition effects, and survivorship bias.

Genome wide association analysis provided additional insight into the genetic structure of heart score. These results indicate that heart score is a polygenic trait influenced by multiple genomic regions of relatively small effect rather than a single major locus. Several chromosomal regions identified overlapped with previous reported QTLs associated with body weight, carcass composition, metabolic traits, and even yearling pulmonary arterial pressure. Notable regions such as chromosomes 3,6,7,9, and 20 demonstrate strong associations with growth, fat deposition, and body composition are present. The identification of genomic regions associated with both cardiovascular remodeling and production traits further supports the hypothesis that biological pathways influence growth and metabolic demand may be contributing to the development of feedlot heart disease.

Together, these findings suggest that feedlot heart disease arises from complex interactions between genetic predisposition and physiological demands associated with modern beef production. Intensive selection for increased growth rate, carcass weight, and feed efficiency may place substantial strain on the cardiopulmonary system of susceptible animals. As a result, continued emphasis on terminal growth traits without consideration of cardiovascular health could inadvertently increase the prevalence of cardiac remodeling in feedlot cattle populations.

Chapter 7 Appendix

JWAS Python Code

```
Pkg.add("StatsPlots")
using JWAS
using JWAS.Datasets
using CSV
using DataFrames
using Statistics
using StatsPlots
using Random

##Clean data using sed command in Terminal
##Input genotype data
genotypes_og = CSV.read("/Users/isabella_k/Desktop/JWAS Folder /JWAS_geno_cl.txt",
DataFrame; delim=" ", header=true, missingstrings=["."])
##Look at how many columns are in your dataset
n_markers_geno = size(genotypes_og, 2) - 1

# Identify columns that start with "Column" to delete blanks
cols_to_remove = filter(name -> startswith(String(name), "Column"), names(genotypes_og))
select!(genotypes_og, Not(cols_to_remove))
# Overwrite the original file
CSV.write("/Users/isabella_k/Desktop/JWAS Folder /JWAS_geno_cl_2.txt", genotypes_og)
genotypes_og = CSV.read("/Users/isabella_k/Desktop/JWAS Folder /JWAS_geno_cl_2.txt",
DataFrame; delim=",", header=true, missingstrings=["."])
n_markers_geno = size(genotypes_og, 2) - 1

genofile= "/Users/isabella_k/Desktop/JWAS Folder /JWAS_geno_cl_2.txt"
genotypes = get_genotypes(genofile; separator=',', header= true, method="BayesC")
####Genotype data is inputed!

# STEP 1: Load phenotype data
# Make sure this has columns like: ID, trait (e.g. HS), sex, age, etc.
phenofile= "/Users/isabella_k/Desktop/untitled folder 3/data.hs"
phenotypes = CSV.read(phenofile, DataFrame; delim=" ", header=false, missingstrings=["."])
rename!(phenotypes, [:ID, :HS, :scorer, :cg, :sire, :grands, :type])
CSV.write("/Users/isabella_k/Desktop/JWAS Folder /data.hs_prep", phenotypes)
phenofile= "/Users/isabella_k/Desktop/JWAS Folder /data.hs_prep"
####STEP 2: Load snp map
map_file = "/Users/isabella_k/Desktop/untitled folder 3/snp_map.csv"
snp_map = CSV.read(map_file, DataFrame; delim=" ", header=true, missingstrings=["."])
```

```

rename!(snp_map, [:marker, :chromosome, :position])
snp_map.marker = string.(snp_map.marker)
CSV.write("/Users/isabella_k/Desktop/JWAS Folder /snp_map_prep.csv", snp_map)
map_file = "/Users/isabella_k/Desktop/JWAS Folder /snp_map_prep.csv"
snp_map = CSV.read(map_file, DataFrame; delim="," , header=true, missingstrings=["."])
#Same length as the genotype headers 69,731.

##STEP 3: Load pedigree

pedfile = "/Users/isabella_k/Desktop/untitled folder 3/complete_ped"
pedigree = CSV.read(pedfile, DataFrame; delim=" " , header=false, missingstrings=["."])
rename!(pedigree, [:ID, :sire, :dam,])
println(pedigree)
pedigree_stk = get_pedigree(pedigree; separator=' ', header=true, missingstrings=["."])

##Make sure all genotyped animals are in pedigree
nrow(pedigree)
first(pedigree, 10)
nrow(phenotypes)
first(phenotypes, 10)

rename!(genotypes_og, names(genotypes_og)[1] => "ID")
pedigree_ids = pedigree.ID
genotypes_ids = genotypes_og.ID
missing_from_pedigree = setdiff(genotypes_ids, pedigree_ids)
println("Missing genotyped IDs not in pedigree: ", missing_from_pedigree)
##only have the animals in the pedigree map_file
valid_ids = Set(pedigree.ID)
genotypes_filt = filter(row -> row.ID in valid_ids, genotypes_og)
##Redo get_genotypes to upload this back in... if all genotyped animals are not found in the
pedigree you will get an error...
missing_geno_ids = setdiff(unique(genotypes_og.ID), pedigree.ID)
CSV.write("/Users/isabella_k/Desktop/JULIA/genotypes_filtered_hs.txt", genotypes_filt;
delim=',', writeheader=true)
genofile = "/Users/isabella_k/Desktop/JULIA/genotypes_filtered_hs.txt"
genotypes = get_genotypes(genofile; separator=',', header= true, method="BayesC")

####Build model
model_equation = "HS = intercept + cg + ID + genotypes"
model = build_model(model_equation)
set_random(model, "ID", pedigree_stk);
####Double check all animals are in all files

phenotype_ids = unique(phenotypes.ID)

```

```

genotypes_filt_ids = unique(genotypes_filt.ID)
pedigree_ids = unique(pedigree.ID)

# Check overlap
missing_from_genotypes = setdiff(phenotype_ids, genotypes_filt_ids)
missing_from_pedigree = setdiff(phenotype_ids, pedigree_ids)
println("Phenotype IDs missing from genotypes: ", missing_from_genotypes)
println("Phenotype IDs missing from pedigree: ", missing_from_pedigree)

valid_ids = intersect(genotypes_filt_ids, pedigree_ids)
phenotypes = filter(row -> row.ID in valid_ids, phenotypes)

###Run analysis
out=runMCMC(model, phenotypes, censored_trait = false, burnin = 15000,
chain_length=60000)

####1. Compute the model frequency for each marker (the probability the marker is included in
the model).

marker_effects_file="results1/MCMC_samples_marker_effects_genotypes_HS.txt"

using DataFrames, CSV, StatsPlots
# Step 1: Run GWAS
# make sure it's the right path
GWAS_results = GWAS(model, map_file, marker_effects_file, header=true, window_size="1
Mb")

CSV.write("/Users/isabella_k/Desktop/JULIA/g=GWAS_results_HS.txt", GWAS_results;
delim=',', writeheader=true)
#GWAS_results3= GWAS(model, map_file, marker_effects_file3, header=true, window_size="1
Mb")

typeof(GWAS_results)
GWAS_results_df_2 = GWAS_results2[1]
GWAS_results_df = GWAS_results[1]

####Check correlation between runs
CSV.write("/Users/isabella_k/Desktop/JULIA/df60k.csv", GWAS_results[1])
df50k = CSV.read("/Users/isabella_k/Desktop/JULIA/df50k.csv", DataFrame; delim=",",
header= true)
CSV.write("/Users/isabella_k/Desktop/JULIA/df60k.csv", GWAS_results2[1])
df60k = CSV.read("/Users/isabella_k/Desktop/JULIA/df60k.csv", DataFrame; delim=",",
header= true)

CSV.write("/Users/isabella_k/Desktop/JULIA/df70k.csv", GWAS_results3[1])

```

```

df70k = CSV.read("/Users/isabella_k/Desktop/JULIA/df70k.csv", DataFrame; delim=",",
header= true)

x = df60k.WPPA
y= df70k.WPPA

corr = cor(x, y)
println("Pearson correlation of genetic variances (50k vs 60k): ", round(corr, digits=5))
# Step 2: Calculate proportion of genetic variance explained
GWAS_results_df[!, :prGenVar] = GWAS_results_df.estimateGenVar ./
sum(GWAS_results_df.estimateGenVar)

# Step 3: Build plotting dataframe
manhattan_df = DataFrame(
CHR = parse.(Int, GWAS_results_df.chr), # Only if chr is String
BP = GWAS_results_df.start_SNP,
PV = GWAS_results_df.prGenVar
)
sorted_df = sort(manhattan_df, :PV, rev=true)
println(first(sorted_df, 10))

# Step 4: Sort and compute cumulative basepair position
sort!(manhattan_df, [:CHR, :BP])

# Initialize cumulative BP column
manhattan_df.cBP = zeros(size(manhattan_df, 1))

offset = 0

for chr in unique(manhattan_df.CHR)
chr_rows = manhattan_df.CHR .== chr
manhattan_df.cBP[chr_rows] .= manhattan_df.BP[chr_rows] .+ offset
offset = maximum(manhattan_df.cBP[chr_rows]) + 20_000_000 # Add 1Mb buffer between
chromosomes
end
println(first(manhattan_df, 20))
# Step 5: Plot Manhattan
import Pkg
Pkg.add("StatsPlots")

Pkg.add("ColorSchemes")
using StatsPlots

# Generate a color palette alternating between two colors (e.g., blue and orange)

```

```

chromosomes = sort(unique(manhattan_df_ppa.CHR))
nchr = length(chromosomes)
Random.seed!(1234)
palette = distinguishable_colors(nchr)
chr_color_map = Dict{chromosomes[i] => palette[i] for i in 1:nchr}
colors = [chr_color_map[c] for c in manhattan_df_ppa.CHR]

# Map each chromosome to its color
chr_color_map = Dict{chromosomes[i] => palette[i] for i in 1:nchr}
colors = [chr_color_map[c] for c in manhattan_df.CHR]

# Calculate chromosome midpoints for labeling
chr_midpoints = [mean(manhattan_df.cBP[manhattan_df.CHR .== c]) for c in chromosomes]

@df manhattan_df:PV
genvar_plot = @df manhattan_df scatter(
:cBP, :PV,
color = colors,
legend = false,
markersize = 3,
xlabel = "Genomic Position",
ylabel = "Proportion of Genetic Variance",
title = "Manhattan Plot of Genomic Windows (Genetic Variance)",
grid = true,
framestyle = :box,
xticks = (chr_midpoints, string.(chromosomes)),
xrotation = 60,
size = (2400, 800),
margin = 15Plots.mm,
)
# Optional: Add horizontal threshold line
hline!(genvar_plot, [0.002], color=:red, linestyle=:dash, label="Threshold = 0.002")

##Posterior probability: confidence not magnitude
using StatsPlots, DataFrames

# Step 2: Use Posterior Probability of Association (PPA) directly
manhattan_df_ppa = DataFrame(
CHR = parse.(Int, GWAS_results_df.chr), # Convert chromosome from String to Int if needed
BP = GWAS_results_df.start_SNP,
PV = GWAS_results_df.PPA_t # Use the PPA column here (adjust if your column name differs)
)

# Step 3: Sort and compute cumulative basepair position
sort!(manhattan_df_ppa, [:CHR, :BP])

```

```

manhattan_df_ppa.cBP = zeros(size(manhattan_df_ppa, 1))

offset = 0
for chr in unique(manhattan_df_ppa.CHR)
chr_rows = manhattan_df_ppa.CHR .== chr
manhattan_df_ppa.cBP[chr_rows] = manhattan_df_ppa.BP[chr_rows] .+ offset
offset = maximum(manhattan_df_ppa.cBP[chr_rows]) + 15_000_000 # 1Mb buffer between
chromosomes
end

println(first(manhattan_df_ppa, 20)) # Preview first 20 rows

# Step 4: Plot Manhattan

chromosomes = sort(unique(manhattan_df_ppa.CHR))
nchr = length(chromosomes)

Random.seed!(1234)
palette = distinguishable_colors(nchr)
chr_color_map = Dict{chromosomes[i] => palette[i] for i in 1:nchr}
colors = [chr_color_map[c] for c in manhattan_df_ppa.CHR]

chr_midpoints = [mean(manhattan_df_ppa.cBP[manhattan_df_ppa.CHR .== c]) for c in
chromosomes]

PPA_plot = @df manhattan_df_ppa scatter(
:cBP, :PV,
color = colors,
legend = false,
markersize = 3,
xlabel = "Genomic Position",
ylabel = "Posterior Probability of Association (PPA)",
title = "Manhattan Plot of Genomic Windows (PPA)",
grid = true,
framestyle = :box,
xticks = (chr_midpoints, string.(chromosomes)),
xrotation = 60,
size = (2400, 800),
margin = 15Plots.mm
)
hline!(PPA_plot, [0.5], color=:red, linestyle=:dash, label="Threshold = 0.5")
savefig(PPA_plot, "/Users/isabella_k/Desktop/JULIA/PPA_plot.png")

savefig(genvar_plot, "/Users/isabella_k/Desktop/JULIA/genvar_plot.png")

summary_df = DataFrame(

```

```
CHR = parse(Int, GWAS_results_df.chr), # chromosome as Int
BP = GWAS_results_df.start_SNP, # base-pair position (window start)
Window = GWAS_results_df.window, # window ID
Trait = GWAS_results_df.trait, # trait name (optional)
EstimateGenVar = GWAS_results_df.estimateGenVar,
StdGenVar = GWAS_results_df.stdGenVar,
ProportionGenVar = GWAS_results_df.prGenVar, # prGenVar column
WPPA = GWAS_results_df.WPPA, # window posterior probability
PPA_t = GWAS_results_df.PPA_t # p
```