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ELUCIDATING THE MECHANISMS DRIVING ADVERSE OUTCOMES IN RACIALIZED
PERINATAL POPULATIONS

A Dissertation Presented

By

Esther A. Boama-Nyarko

Submitted to the Faculty of the

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DOCTOR OF PHILOSOPHY

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POPULATION HEALTH SCIENCES

REVIEWER PAGE

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This work was undertaken in the Morningside Graduate School of Biomedical Sciences

Doctoral Program in Population Health Sciences

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February 20, 2025

DEDICATION

To my Family & Village.

For their support, prayers and encouragement. Thank you.

And a special dedication to my mother, Joana Kyereh.

The unfathomable pain of her death pushed me to seek the next step in my life's journey and it lead me to this education. Working through that dark time has shaped how I face every challenge since her passing. Therefore, I want to honor her as an irreplaceable example of strength and recognize her spirit as a guiding light in all my pursuits.

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ABSTRACT

Adverse obstetric outcomes, such as hypertensive disorders, preterm birth, and depression, disproportionately affect marginalized populations in the US and contribute to long-term health risks like cardiovascular disease (CVD). Racism and chronic stress are drivers of these inequities, yet the biological pathways linking them to perinatal health are underexplored. Allostatic load (AL), a cumulative measure of biological wear and tear from chronic stress, offers a potential tool for exploring these relationships and informing clinical care.

We synthesized existing studies that measured AL in pregnancy, explored the feasibility of identifying AL biomarkers in clinical data, and examined the association between a biomarker-based index, modeled after AL, and adverse obstetric outcomes that impact CVD risk. We also incorporated iterative feedback from a working group of perinatal professionals. The scoping review identified 22 biomarkers and a refined index was developed using a subset. The most common combination for an index included six biomarkers, which included blood pressure and albumin. While the refined index was not significantly associated with adverse obstetric outcomes, the results highlighted stable partnerships as a protective factor.

Exploring the relationship between AL and health inequities in perinatal populations is complex, especially using retrospective clinical data. Challenges include missing data and the inconsistency in how data is documented for clinical care compared to research. Despite these limitations, there is a need to refine AL indices further and explore systematic inequities and the biological pathways that may impact perinatal outcomes. These findings may inform the development of helpful interventions.

Table of Contents

REVIEWER PAGE	ii
ACKNOWLEDGEMENTS	iv
ABSTRACT	vi
LIST OF TABLES	viii
LIST OF FIGURES	viii
LIST OF ABBREVIATIONS	ix
PREFACE	x
CHAPTER I	1
CHAPTER II	8
CHAPTER III	37
CHAPTER IV	52
CHAPTER V	73
APPENDIX A-	83
REFERENCES	85

LIST OF TABLES

Item	Description	Page
Table 1.1	Scoping Review Questions and Sub questions.	28
Table 1.2	Characteristics of Studies Measuring AL in Pregnancy	29
Table 1.3	Specific Biomarkers used in Previous AL indices in Pregnant Individuals	31
Table 1.4	Operationalization of AL Biomarkers from Reviewed Studies	33
Table 1.5	Candidate Biomarkers for an AL index for pregnancy	36
Table 2.1	Demographics in Sample	50
Table 2.2	Biomarkers Available in Sample	51
Table 3.1	Cutoffs for Cardiometabolic Index Using Sample Population	70
Table 3.2	Frequency of Adverse Obstetric Outcomes	10
Table 3.3	Cutoff Values and Distribution of Biomarkers in Study Sample	71
Table 3.4	Study Demographics by Adverse Outcome Status	71
Table 3.5	Association between a cardiometabolic index using sample cutoffs and adverse obstetric outcomes	72
Table 3.6	Association between a cardiometabolic index using clinical cutoffs and adverse obstetric outcomes	72

LIST OF FIGURES

Item	Description	Page
Figure 1.1	PRISMA diagram for included and excluded studies	27
Figure 2.1	Merged Data from Data lake	49

LIST OF ABBREVIATIONS

Allostatic load (AL)

Cardiovascular Diseases (CVD)

Catherine Carr (CWC)

Clevanne Julce (CJ)

Confidence Intervals (CI)

C-reactive protein (CRP)

Dehydroepiandrosterone-sulfate (DHEA-S)

Diastolic blood pressure (DBP)

Electronic Medical Record (EMR)

Esther Boama-Nyarko (EBN)

Glycosylated/glycated hemoglobin (HbA1c)

High-density lipoprotein (HDL)

Hypothalamic-pituitary-adrenal (HPA)

International Classification of Disease Tenth Revision (ICD -10)

Martha Zimmermann (MZ)

Population Health Sciences (PHS)

Population and Quantitative Health Sciences (PQHS)

Systolic blood pressure (SBP)

Total cholesterol (TC)

United States (US)

Waist-hip ratio (WHR)

PREFACE

Materials from this dissertation that have been submitted to scientific journals or conferences as of February 20, 2025, are as follows:

Chapter II of this dissertation is under review as:

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CHAPTER I
INTRODUCTION

1.1 Morbidity and Mortality in High-Risk Perinatal Individuals: A Public Health Crisis

Some individuals experience short and long-term morbidity as a result of being pregnant and giving birth. At times, these complications result in mortality, with individuals from racially and ethnically marginalized groups (e.g., Hispanic/Latina/e/x, Native American/Indigenous, and Black individuals) facing a higher risk. For example, Black perinatal individuals in the United States (US) experience a disproportionately higher risk for adverse pregnancy outcomes, including mortality. Compared to their White counterparts, they have increased rates of preterm birth (1-3) and have the highest rates of nearly all severe morbidity indicators (4). Black individuals are three to four times more likely to die in the perinatal period than their White counterparts and continue to experience the high mortality rates even compared to other racially and ethnically marginalized populations (5, 6). Native American/Indigenous perinatal individuals also have elevated morbidity and mortality compared to their white counterparts, especially those who live in rural areas (7). Cardiovascular diseases (CVD) and other pregnancy-related complications are a leading cause of mortality in the US, and Black and other racial-ethnic minoritized perinatal individuals are disproportionately affected (8). Many complications and adverse outcomes from pregnancy (e.g., hypertension, preeclampsia, and preterm birth) are recognized risk factors for CVD (1-3, 9-12). Minoritized individuals, such as Black and Native American perinatal individuals, have increased rates of pregnancy-related heart attack, peripartum cardiomyopathy, and pulmonary embolism than their White counterparts, even accounting for healthcare access as well as individual and socioeconomic factors (9). Hypertensive disorders of pregnancy, such as preeclampsia, are also highest in Black individuals. Black individuals are more likely to begin pregnancy with chronic hypertension and develop mild, severe, or superimposed preeclampsia compared to their other racial and ethnic

counterparts (13). Similarly, Asian/Pacific Islander perinatal individuals are most at risk for acute cardiovascular complications during labor and delivery (14, 15).

Aside from physical health, mental health morbidity is also disparate for racial-ethnic minoritized individuals. Perinatal mood and anxiety disorders, like depression, are associated with obstetric outcomes like preterm birth and are also a leading cause of preventable perinatal mortality (16-18). While depression is common in the perinatal period (19, 20), the burden of underdiagnosed and undertreated perinatal mood and anxiety disorders looms largest for racial-ethnic minoritized perinatal individuals. They are twice as likely as their white counterparts to experience mental health conditions, such as postpartum depression, but only half as likely to receive the necessary treatment and care (21). Depression is also emerging as a nontraditional risk factor for CVD (22) and is known to be associated with incident risk of CVD as well as worsening the prognosis (23, 24).

1.2 Structural drivers of inequities

The drivers of the inequities in the risk of morbidity and mortality are rooted in racism (25, 26). These inequitable outcomes are the result of segregation, discrimination, and historical laws (e.g., redlining) that were created to oppress minoritized people and women in the US (26-29). Racism is deeply embedded in systems and policies and entrenched in practices that perpetuate widespread oppression of marginalized people. Racism is a source and fundamental cause of significant health inequities (30). It drives inequitable education, employment, and housing outcomes, especially among Black perinatal individuals (26). Social determinants of health and other individual factors alone are limited and inadequate explanations for these dire statistics. It has been reported that Black perinatal individuals with a completed college education have an increased risk of pregnancy-related mortality as compared to their White

counterparts with less than a completed high school diploma education (25). However, despite the strong linkage with increased perinatal morbidity and mortality, the mechanisms through which racism in all its forms impacts perinatal health are still relatively undefined and unknown. One mechanism that is gaining traction to understand how racism and discrimination manifest poor health is allostatic load.

1.3 Chronic Stress and Allostatic Load

Allostatic load (AL) is a growing area of interest for understanding health inequities and offers promise for understanding and improving perinatal outcomes. There is a growing body of epidemiological work examining associations between stress (e.g., chronic stress and psychosocial stress) and perinatal health inequities (26, 31-34). Experiencing racism triggers a stress response, where the body's reactive biological processes cause premature aging and increase the risk of chronic disease and death (35, 36). The biological "wear and tear" of racism has been studied as the weathering hypothesis. Coined by Arline Geronimus, weathering describes how chronic stress (significantly exacerbated by racism, discrimination, social disadvantage, and unjust policies that impact health and wellbeing) wears down the body's systems and biologically ages it. In contrast to chronological age, which tracks the amount of time from birth, biological aging encompasses the multifactorial cellular and molecular processes that underlie disease risk and biological functioning (37). This mechanism may account for the disparate health outcomes in disease risk seen in racially and ethnically minoritized individuals, especially during the perinatal period. According to the weathering hypothesis, chronic stress before pregnancy may contribute to adverse perinatal outcomes, especially for racially and ethnically minoritized individuals who are usually at increased risk of these complications (35).

AL is one mechanism to measure the impact of weathering and biological aging. It quantifies disease risk by measuring the cumulative burden of chronic stress on the body and brain's biological systems (38). An important distinction is that AL does not insinuate biological foundations for health inequities; instead, it proposes quantifying the cumulative effects of marginalization and stress using a composite biological measure known as an AL index. AL is higher in Black perinatal individuals, is connected with older age and brain decline, and contributes to all-cause mortality in non-perinatal Black populations(38-40). However, perinatal individuals, especially during pregnancy, are often excluded from AL research due to the complexity of accurate measurement (40). Variables included in AL indices, known as biomarkers, may change in pregnancy as part of the regular physiological changes in response to placenta-derived and other hormones (41). Studies for perinatal populations often rely on AL that is measured preconception or post-delivery, leaving out pregnancy. Pregnancy can be a time in the perinatal period when underlying risks can exacerbate adverse obstetric outcomes. Also, although research has examined AL with various biomarkers, there still has not been much progress made toward a comprehensive AL index that is clinically relevant and feasible for routine pregnancy care.

1.4 Specific Aims

This research aims to identify a potential combination of biomarkers to comprise an index patterned after AL that is also informed by routine pregnancy care. The specific aims of the dissertation are as follows:

Aim 1: Synthesize existing data on using AL biomarkers in pregnant populations. This research is a scoping literature review about measuring AL in pregnancy using biomarkers and incorporating iterative feedback from a working group of perinatal professionals (n=6). The

scoping review will describe 1) the physiological systems most involved in AL during pregnancy, 2) the different biomarkers used to measure AL in pregnant individuals, 3) methods used to account for physiologic adaptations during pregnancy, and 4) how AL research in pregnant populations has examined racial/ethnic differences.

Aim 2: Examine the feasibility of using indicators of an AL index in a sample of perinatal individuals accessing routine clinical care. This exploratory analysis examines how feasible it is to identify the components of an AL measure in the diagnostics of routine pregnancy care using clinical data from a repository in a large healthcare system.

Aim 3: Assess the association between a biomarker-based health index modeled after AL, and adverse obstetric outcomes among perinatal individuals. Using diagnostic and assessment data from a large healthcare system, this research examines the association between a cardiometabolic health index patterned after AL with adverse obstetric outcomes (e.g., depression, preterm birth, and hypertensive disorders of pregnancy). The hypothesis is that perinatal individuals with marginalized racial and ethnic identities will fare worse on this index compared to their White counterparts.

1.5 Importance and Public Health Significance

Morbidity and mortality in the perinatal period is a major public health concern however there may be opportunities to address health concerns especially for individuals who are racially and ethnically minoritized. Chronic stress has been recognized as a driving contributor to health inequities and there is growing interest in using measures such as AL to better understand how stress contributes to adverse outcomes, especially in perinatal populations (34). Despite the growing evidence of how AL can be used to measure the impact of stress in perinatal

individuals, translating the insights into tools for clinical practice and refining measures to be more relevant for perinatal individuals remains a significant challenge and underexplored (42-44).

The research in this dissertation aims to increase understanding of the mechanisms and pathways that lead to health inequities in perinatal care. By focusing on how to measure and interpret the biological impacts of chronic stress, this research provides a foundation for the potential of developing clinical tools that can be used to improve care. Such tools would be helpful for addressing health for marginalized perinatal individuals, who are disproportionately face disparate health outcomes. This research is a critical first step in addressing complex and nuanced questions about perinatal health inequities and creating practical solutions to reduce them.

CHAPTER II

SYNTHESIZE EXISTING DATA ON USING AL BIOMARKERS IN PREGNANT POPULATIONS

ABSTRACT:

Introduction: Allostatic Load (AL), a cumulative measure of chronic stress exposure, is often quantified using an index of biomarkers (e.g., blood pressure, cortisol, C-reactive protein). AL provides valuable insights into the mechanisms driving health inequities in pregnancy. However, pregnancy-specific physiological changes and advancing gestation impact biomarker levels, posing challenges to measuring AL during pregnancy. This research synthesizes existing data on AL biomarkers used in pregnant populations.

Methods: A scoping review was conducted using PubMed, Scopus, PsycINFO, and CINAHL to identify studies. The final studies identified 1) included pregnant individuals (50% or more aged 18–50 years), 2) measured AL, and 3) used indices with more than one biomarker. An iterative consultation process with perinatal professionals (n=6) supplemented the review to identify clinically relevant and feasible biomarkers.

Results: Ten studies met the inclusion criteria, with sample sizes ranging from 30 to 4,508 participants. Biomarker selection varied significantly across studies, and indices included between five and 12 biomarkers. Commonly represented systems included cardiovascular, metabolic, inflammatory, and neuroendocrine. Six studies adjusted for gestational age variations, and four addressed differential stress exposure by race/ethnicity. After consultation with perinatal professionals, 14 candidate biomarkers were identified for inclusion in a clinically relevant AL index for pregnancy.

Conclusion: AL indices for pregnancy largely mirror those for nonpregnant populations but must address gestational changes and stress disparities. Future research should refine AL measurement in pregnancy, account for racial/ethnic inequities, and explore clinical applications to improve perinatal care and outcomes.

INTRODUCTION

Exposure to chronic stressors, such as social and economic inequities, increases the risk of adverse health outcomes, death (35, 45), and maladaptive physiological wear and tear (46). The “wear and tear” on the body and the brain from accumulated stress and other arousing stimuli is known as Allostatic load (AL) (47). Measures of AL, also called AL indices, can be used to understand disease risk by quantifying the cumulative burden of chronic stress on the body’s biological systems (e.g., cardiovascular, metabolic, inflammatory) from repeated exposure to adverse stimuli (e.g., social, economic, and environmental) (46, 48, 49). The weathering hypothesis posits that chronic exposure to social, political, and economic disadvantage leads to premature declines in physical health (35, 50). Individuals in the US who experience racism (e.g., Black and Hispanic/Latino/a/x individuals) exhibit a higher prevalence of stress, with multiple reported stressors compared to their white counterparts (51), which are reflected in higher average AL scores compared to more advantaged populations (39).

AL was initially measured by an index of ten biomarkers representing three different systems: 1) neuroendocrine biomarkers (Dehydroepiandrosterone-Sulfate (DHEA-S), Epinephrine, Norepinephrine, cortisol), 2) cardiovascular biomarkers (Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Total Cholesterol (TC), High-Density Lipoprotein (HDL) Cholesterol), and 3) metabolic biomarkers (Glycosylated Hemoglobin (HbA1c), Waist-Hip Ratio (WHR)) (49). Studies focused on the AL index have expanded to include other biomarkers that can increase the understanding of how AL is associated with various health outcomes among different populations (38, 52-54). Despite the advancements in AL measurement and premature health deterioration associated with inequities in perinatal outcomes (34), pregnant populations continue to be underrepresented in AL research.

This gap is significant because pregnant individuals who experience chronic stress are at an increased risk of adverse birth outcomes, such as having preterm birth and delivering low birth weight neonates (19, 34, 55). Although AL indices account for some inequities in obstetric outcomes, the data on AL in pregnancy are limited. Since its conceptualization, there has been variation in how AL indices have been constructed, and this is particularly relevant to research concerning pregnant individuals (53, 56). Pregnant individuals are often excluded from population studies that use AL measurements due to the concern of pregnancy-specific physiologic changes to AL-related biomarkers during pregnancy through the first year postpartum (perinatal) period (57, 58). During pregnancy, physiological adaptations in AL-relevant biomarkers (e.g., changes in blood pressure, epinephrine, and cortisol) occur naturally to promote optimal fetal growth (59). Also, although AL is associated with some adverse health outcomes during pregnancy, the mechanisms that drive increased risk among minoritized individuals are still unclear. For example, Black perinatal individuals are up to three times more likely to die during the perinatal period compared to their White counterparts (60). Understanding the relationship between AL and adverse health outcomes during pregnancy can help elucidate underlying mechanisms that drive inequities in perinatal and fetal outcomes.

Studies that have examined AL in pregnant and nonpregnant individuals have indicated a need for careful biomarker selection due to heterogeneity in the operationalization of AL across studies (38, 52, 54, 56, 59). Altered biomarker profiles in pregnancy raise questions concerning whether AL can represent the cumulative impact of lifetime stress rather than just stress due to pregnancy and the challenges of the timing of exposure assessment. However, there is a dearth of research that disentangles the impact of physiological changes associated with pregnancy and advancing gestation from AL. There is a need to understand what biomarkers best quantify

impacted biological systems and to consider other necessary factors when constructing an AL index to appropriately measure the impact of accumulated chronic stress in pregnant individuals. This study aims to describe 1) how AL has been measured in pregnant individuals, 2) the association between AL and adverse pregnancy outcomes (e.g., depression and hypertensive disorders of pregnancy), and 3) which methods may help elucidate racial/ethnic inequities in stress exposure.

METHODS

Scoping Review

Identifying the Research Question

The objective of this scoping review was to describe what the current AL literature includes about measuring AL in pregnancy. Specifically, we examined the following questions:

1. How is AL assessed among pregnant individuals?
2. What physical and health outcomes/indicators have been examined with AL when researching pregnant individuals?
3. Are there any comparisons between pregnant and nonpregnant populations?
4. How does AL research in pregnant populations examine racial/ethnic differences?

See Table 1.1 for the detailed questions examined in this scoping review.

Identifying relevant studies

Our scoping review was guided by the framework presented by Arksey and O'Malley and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) (61, 62). We developed a comprehensive search strategy with a medical

librarian (CWC) from a public academic health sciences center. We built and executed a comprehensive and reproducible search to identify AL research specific to pregnant individuals in English and involving human subjects. The medical librarian searched the electronic databases (PubMed, Scopus, PsycINFO, and CINAHL) on January 6, 2023. These search databases included both biomedical and social science literature. Key search terms included: Allostatic, or allostatic; weathering hypothesis; psychosocial stressor(s); pregnancy, perinatal, and childbearing. A snowball search was then conducted on May 17, 2023, to capture any new citations for inclusion. A complete description of our search strategy is found in Appendix A.

Study Selection

After removing duplicates from the initial search, two independent reviewers (EBN and CJ) reviewed titles and abstracts to assess first-pass eligibility. All eligible studies included: 1) pregnant adult individuals (with more than 50% of the sample 18-50 years of age), 2) allostatic load measured in pregnant individuals, 3) a cumulative allostatic load (AL) index (more than one biomarker), and 4) original research reports. Since AL is commonly operationalized as a composite measure of the dysregulation of multiple systems, we examined the literature to include any AL measures with more than one biomarker (63, 64). Articles were excluded if (1) age ranges only included individuals younger than 18 years or older than 50 years, (2) they did not include pregnant individuals, (3) there was a lack of AL measure with physical biomarkers like anthropometric measures, vital signs, or laboratory studies (e.g., used subjective measures of psychosocial stress or surveys instead of using biomarker-based AL) or they did not have a cumulative AL measure, or (4) articles are not published in English. The details of the final studies included for extraction are provided in Figure 1.1.

Data Extraction

Article abstracts were reviewed and extracted using Covidence review software (65). We created and used a data extraction tool based on the Covidence extraction template. The extraction tool also included but was not limited to questions about authors, the country where the study was conducted, population, study design, details on how AL was defined and operationalized, the data source for biomarker collection, and any ethical considerations related to the area of study. EBN and CJ piloted the extraction process by reviewing two articles and comparing results. This initial pilot allowed discussion of any relevant modifications to the extraction tool before extracting data from the remaining full texts of articles. After the pilot, additional data collection items were added, and the reviewers used the enhanced and finalized data abstraction tool for all studies included in the full-text review. Inconsistencies between the reviewers at every stage of the scoping review were discussed and resolved through discussion and consensus until all titles and abstracts were reviewed and data was abstracted from the final included studies. Additional protocols included discussing with a third reviewer (MZ) if coding disagreements between the two reviews required an additional person for reconciliation.

Data Synthesis and other methods

A list of biomarkers used in AL indices across each study was compiled. Biomarkers were categorized based on standard biological system designation from previous studies (53). Common biomarkers used in multiple studies were organized and tabulated.

Consulting a Working Group of Perinatal Professionals

This study incorporated iterative feedback from a working group of five perinatal professionals from the Maternal-Fetal Medicine, Obstetrics and Gynecology, and Family

Medicine departments in UMass Memorial Health's clinical healthcare system. We also consulted an outside obstetrics and gynecology professional from the United Kingdom who is researching the impact of stress on pregnant women, health disparities, and fetal health outcomes. We discussed candidate biomarkers gleaned from our scoping review in group and individual meetings. We received feedback on these candidate biomarkers' usability, utility, and feasibility to comprise an optimal AL index. Our index of candidate biomarkers was synthesized from common biomarkers from the literature and biomarkers in perinatal care that are not seriously impacted by gestation. We also discussed the timing of when it is best to measure these biomarkers in pregnancy and other clinical considerations around defining high-risk for each biomarker.

RESULTS

Overview of Scoping Review Results

Study characteristics

Ten articles met the inclusion criteria. Study characteristics are displayed in Table 1.2. The total sample size across all ten studies was 11,505 pregnant individuals with ranges between 30 and 4,508. The studies were published between 2013 and 2023 and conducted in the United States.

Question 1: How is AL assessed among pregnant individuals?

AL Biomarker Sources

Table 1.2 details all the biomarker data sources in each study. Biomarkers were analyzed from freshly collected blood and plasma samples (66-71), saliva (66), and urine (72), vital signs (e.g., blood pressure)(40, 41, 66-71, 73, 74), and anthropometric measures (e.g., BMI) (41, 66-

68, 70, 72, 74). Other data sources included using stored specimens and lab data collected as part of community health initiatives (i.e., National Health and Nutrition Examination Survey (NHANES) mobile examination center (MEC) data).

Biological systems represented in AL measures

Biological systems represented in AL research for pregnant individuals included cardiovascular, metabolic, anthropometric, inflammatory, and neuroendocrine. All ten studies had biomarkers that represented cardiovascular and metabolic systems (40, 41, 66-71, 73, 74). Seven studies specified an anthropometric biomarker (41, 66-68, 70, 73, 74). Biomarkers in the inflammatory system were used in AL indices for nine studies (40, 41, 66-70, 73, 74). Biomarkers that represented neuroendocrine systems were represented in only three studies (41, 66, 69, 71).

Biomarkers contributing to AL indices.

Various combinations of AL biomarkers represented different biological systems and comprised the AL index across the ten studies (Table 1.3). The total number of AL biomarkers used ranged from 5 to 12 per study. There was heterogeneity among the different studies in biomarkers used to operationalize AL, with Systolic Blood Pressure as the only biomarker used in all ten studies. Common biomarkers that were used in at least half of the studies included Systolic Blood Pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), C-reactive protein (CRP), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), Triglycerides, Glucose and Interleukin-6 (IL-6). Biomarkers such as the homeostatic model for insulin resistance (HOMA-IR), Leptin, Dehydroepiandrosterone-sulfate (DHEA-S),

homocysteine, and tumor necrosis factor-alpha (TNF-a) were only used in one study (Table 1.3) (40, 66, 68, 69, 71).

Timing of measurements in pregnancy

Six studies measured AL biomarkers in the first trimester (0 to 13 weeks gestation) (41, 66-68, 73, 74). Eight studies included AL biomarkers measured in the second trimester (41, 66-71, 74). Four studies measured AL biomarkers in the third trimester (41, 66, 69, 74). Two studies reported using early pregnancy AL measures to reflect the comparable measures of each biomarker more closely with their preconception measures than later in pregnancy (67, 68). Two studies measured AL biomarkers at the second and third trimesters to explore the relationship between AL and gestational age (69, 71). Studies considered the impact of gestational age on AL's association with outcomes by accounting for gestational age in statistical models in various ways. One study specifically adjusted for the gestational week when the biomarkers were measured (69). One study examined each gestational month separately for all biomarkers in the analysis, (41) and another conducted a separate sensitivity analysis where authors adjusted for gestational age but found that it did not influence the study results (70). The authors of the remaining seven studies did not specifically choose gestational age times but instead used retrospective data and were thus subject to when the original data was collected (41, 66-71, 73, 74).

AL operationalization

The studies included operationalized AL indices differently (Table 1.4). Biomarkers were either standardized to their distribution in the collected study sample (66, 69-71, 73, 74) or standardized using the sample distribution according to a nationally represented dataset using

quartiles (40, 41, 67, 68). Some studies recommended clinical cutoffs for specific biomarkers (i.e., SBP and DBP) (74). All AL indices for the included studies summarized their index with a score. These measures included a sum score of individual biomarkers, a summary score of the biological systems that the biomarkers belong to, or z-scores.

Question 2: What physical and mental health outcomes/indicators have been examined in association with AL when researching pregnant individuals?

In seven studies, AL was used to explore relationships with relevant health outcomes for pregnant individuals. These studies examined AL as an exposure to associations with various maternal and infant outcomes. Outcomes included sleep quality (68), pregnancy length (i.e., gestational age in weeks at birth) (70), preterm birth (74), birth weight (70, 71), preeclampsia (67), child peripheral blood mononuclear cell mitochondrial content and bioenergetic capacity (66), gestational diabetes (69), and cardiovascular disease (73). Another study found that the AL index was not associated with perceived stress and perinatal distress (68).

In two studies, AL was associated with cardiovascular disease risk, hypertensive disorder of pregnancy (e.g., with higher odds of preeclampsia), and cardiometabolic disorders (67, 68, 73, 74). AL was also positively associated with poor sleep quality (68). One study indicated elevated AL in pregnant individuals with gestational diabetes and that these elevated AL levels were associated with elevated AL indices for their infants measured through fetal cord blood (70). One study, however, did report that BMI, SBP, DBP, Triglycerides, Insulin, and High-Sensitivity CRP were strongly associated with adverse pregnancy outcomes such as hypertensive disorders in pregnancy (74).

Question 3: Are there any comparisons between pregnant and nonpregnant populations?

Two studies compared the differences in AL between pregnant and nonpregnant individuals. These studies explored the validity of measuring AL as a reflection of chronic stress in pregnant individuals compared to nonpregnant individuals (40, 41). The first study found significant differences in the mean level of each AL biomarker used in their index (i.e., CRP, Albumin, TC, HDL, Creatinine, homocysteine, HbA1c, SBP, DBP, pulse) between pregnant and nonpregnant women (40). In some of these biomarkers (i.e., CRP, TC, HDL cholesterol, and pulse), the mean values for pregnant women were statistically significantly higher. In contrast, the mean values were statistically significantly lower in other biomarkers (i.e., Albumin, Creatinine, HbA1c, Homocysteine, SBP, and DBP).

The second study found differences in the adjusted means and standard errors for each of the 10 AL biomarkers (i.e., SBP, DBP, BMI, CRP, TC, HDL, Triglycerides, Glucose, Pulse, and HbA1C) across gestational months. Compared to the average AL score in nonpregnant individuals, AL steadily decreased from month one to month four before increasing from month five through the ninth month of gestation in pregnant individuals. The authors in this study included gestational age as an explanatory variable in linear modeling between a gestational month and the biomarker. Once the authors included gestational age in the model, the AL score was comparable between pregnant and nonpregnant individuals (41).

Question 4: How does AL research in pregnant individuals examine racial/ethnic differences?

Half of the studies in our scoping review looked at the impact of race/ethnicity in their statistical analyses (40, 68, 71, 73, 74). Some studies adjusted for race/ethnicity to remove the effect as a confounder (41, 66, 69, 70). One study did not examine race or ethnicity as a covariate because the study did not detect an association between race and preeclampsia (67). Racial and

ethnic comparisons were mainly between Black-white counterparts who were non-Hispanic. Two studies found that Black pregnant individuals had lower AL than their white counterparts (40, 71). One study observed that Black pregnant individuals had higher AL than their white counterparts, but the results were not statistically significant (68). Another examined the risk of cardiovascular outcomes using mediation and moderation analyses. The authors found that across race/ethnicity, AL was associated with cardiovascular disease risk (CVD) risk and that non-Hispanic Black individuals had higher AL and were more likely to be at risk for CVD compared to their white counterparts (73).

Optimal candidate biomarkers for an AL index in pregnancy

After several discussions with members of our working group, we synthesized a list of 14 biomarkers that incorporate biomarkers identified in the literature along with easily accessible measures that can be collected as part of pregnancy care (see Table 1.5). The list of candidate biomarkers includes cardiovascular and metabolic biomarkers, two inflammatory biomarkers, an anthropometric biomarker, and one neuroendocrine biomarker to represent the autonomic nervous system, which is a primary mediator involved in the cascade of events. Our perinatal professionals discussed that the majority of AL-relevant biomarkers, outside of blood pressure, BMI, and Glucose (collected as part of the glucose tolerance test), are usually less available as they are collected to monitor patients at higher risk for adverse obstetric outcomes. Therefore, they caution researchers in using this entire list of biomarkers based on the outcome they are investigating. One concern is that biomarkers that meet or exceed clinical thresholds may be misinterpreted as an indication of AL when they indicate an acute or chronic health disorder. For example, two professionals expressed concern about using blood pressure in an index that compared the association between AL and preeclampsia because having high blood pressure

over a specific threshold is a clinical indication of the disorder. However since AL is a composition of biomarkers, there may need to be additional methods to standardize individual biomarkers toward the sample average. The working group also suggested measuring biomarkers in the first trimester to assist in establishing a temporal relationship between an AL index and the associated outcome being investigated.

DISCUSSION

We observed that biomarkers used to measure AL in pregnancy predominantly represented the neuroendocrine, cardiovascular, metabolic, and inflammatory systems across all studies. These results are consistent with AL research among nonpregnant populations (49, 75). Also consistent with findings from systematic reviews (52, 56) and other scoping reviews of AL in nonpregnant populations, we observed heterogeneity in AL operationalization (i.e., biomarker and total AL indices), scoring, and methodological variation with biomarkers (52, 56). We identified 22 biomarkers used to measure AL across ten studies with variable combinations of biomarkers included in cumulative AL measures. We also observed results on timing for biomarker collection during pregnancy.

Of the biological systems represented in the included studies, the neuroendocrine system was the least represented. The neuroendocrine response and ensuing hypothalamic-pituitary-adrenal (HPA)-axis dysregulation are necessary to distinguish AL from metabolic syndrome (76). Although some of the biomarkers overlap, AL and metabolic syndrome are conceptually different. Metabolic syndrome is a group of conditions that increases adverse health outcomes (e.g., cardiovascular disease risk and insulin resistance) (77). Therefore, to align with the definition of measuring AL, representing the neuroendocrine system with appropriate biomarkers

should be considered when constructing an AL index for pregnant individuals. The lack of biomarker representation of the neuroendocrine system is consistent with the general literature, as AL index operationalization often needs to show better fidelity to the original concept (78). It has been speculated that poor fidelity to the original concept of AL is due to the fact that the relevant biomarkers, especially for the neuroendocrine system, were frequently unavailable in available data sources (78).

Some biomarkers were only used once in the variable combination of biomarkers for the different AL indices in the ten studies. In some cases, when biomarkers were unavailable, different biomarkers that measure similar effects were selected to replace them. For example, one study replaced waist-hip ratio (WHR), a measure of central adiposity, with pre-pregnancy BMI to reflect a measure of pregnancy-related metabolic risk (70). That study also replaced HbA1C with values from the Glucose tolerance test, the standard test for screening for the most common metabolic disease in pregnancy (i.e., gestational diabetes) (70). Such evidence shows how research has built upon the original biomarkers first used to measure AL, including other secondary and tertiary biomarkers that can be used in relevant populations. Most studies did not mention why specific biomarkers were chosen over others except one. One study explicitly noted that the selected biomarkers were 1) responsive to chronic maternal stress, 2) known to play obligatory roles in the initiation, maintenance, and progression of gestation, fetal development, and birth, and 3) known to mediate the effects of the stress response and its impacts on fetal development (66). We also gleaned from the reviewed articles that routine prenatal care screening tests and measures, like the glucose tolerance test, are being integrated into AL indices. Examining clinically available biomarkers may aid in research towards using AL to

inform future clinical care of pregnant individuals. However, the heterogeneity in biomarkers makes it challenging to make consistent comparisons across studies on pregnancy.

It is important to disentangle the impacts of advancing gestation from the impacts of AL. Our results indicate that measuring AL during early pregnancy is the most common method to reflect the lifetime impacts of stress with minimal interaction from advanced gestation. Some studies used early pregnancy measurements to mirror preconception measures of these biomarkers. Stress experienced before conception is associated with adverse obstetric outcomes (e.g., shorter gestation) (79). However, our review did not substantiate that measuring biomarkers in the first trimester is a standard method for reflecting the impacts of AL with minimized confounding or effect modification from advancing gestation. Our review also indicated the intergenerational impacts of heightened maternal physiological stress during pregnancy on adverse neonatal cardiometabolic health, with one study finding that the maternal AL index was associated with the fetal cord blood AL index (70).

Five of the studies examined racial and ethnic differences in AL. Previous AL literature in nonpregnant individuals has observed higher AL in Black women than their Black male counterparts and white women (35, 80). In contrast, some studies in our review did not observe these trends. Black pregnant individuals were observed to have lower cumulative AL indices than white comparison groups in two studies (40, 71), which contradicts previous research that self-identified nonpregnant individuals who are Black have elevated AL (35, 81). In one study, AL was a partial mediator between race and CVD risk, suggesting AL may be one pathway explaining the relationship between race and health outcomes (73). Our findings suggest that differential exposure to stressors should be accounted for in AL research, even when not looking explicitly at racial/ethnic differences. In the pathway of how chronic stress from marginalization

and disadvantage are associated with disease risk, especially in perinatal individuals, AL plays a mediating role.

Strengths & Limitations

Our study has several strengths. To our knowledge, this is the first scoping review that examines AL explicitly measured in pregnancy and examining its connection to clinical practice. A second strength is the specificity of our criteria (e.g., only including studies that measured AL in pregnancy rather than during preconception or postpartum and studies that included an AL index that represented multiple biological systems, not just exploring individual biomarkers). These criteria allowed us to conclude that pregnant individuals are an understudied population in AL research. Examining the impact of chronic stress as measured by AL in this population has the potential to impact and provide insights on maternal and offspring outcomes, thus exploring the impact on intergenerational health. Next, the search was comprehensive, and the data review and extraction were completed using multiple reviewers who followed a standardized methodology for consensus building that would increase scientific rigor. This study also included guidance and feedback from practicing perinatal professionals on what biomarkers are clinically relevant to standard pregnancy care.

However, one limitation is the small sample size of reviews that met the inclusion criteria. The small size was due to the exclusion of animal models and studies that explored perceived stress instead of the cumulative measure of AL using biomarkers. The excluded studies have contributed imperative conceptual knowledge to the field but were omitted a priori. We excluded animal models a priori because we wanted to assure direct applicability to humans and human pregnancy, thus precluding the complications in extrapolating adaptations in AL

measure from nonhuman animals with unique genetic backgrounds (82). We excluded studies that only measured perceived stress using psychosocial assessments because although AL measures the impact of perceived stress on biological systems, AL research primarily utilizes biological markers, not surveys or scales. Thus, we sought consistency with the nonpregnant literature. Another limitation is that most individuals included in the studies were women, and there was no discussion of other intersectional identities. The lack of information on gender diversity in the sample limits the ability to examine different factors of marginalization beyond racial/ethnic identity. Also, no studies discussed interventions that could impact the adverse obstetric health outcomes associated with AL. However, AL research in the perinatal period is still maturing, and interventions that leverage the measure to improve outcomes in pregnancy and throughout the period may have yet to be fully explored (34).

Future Directions

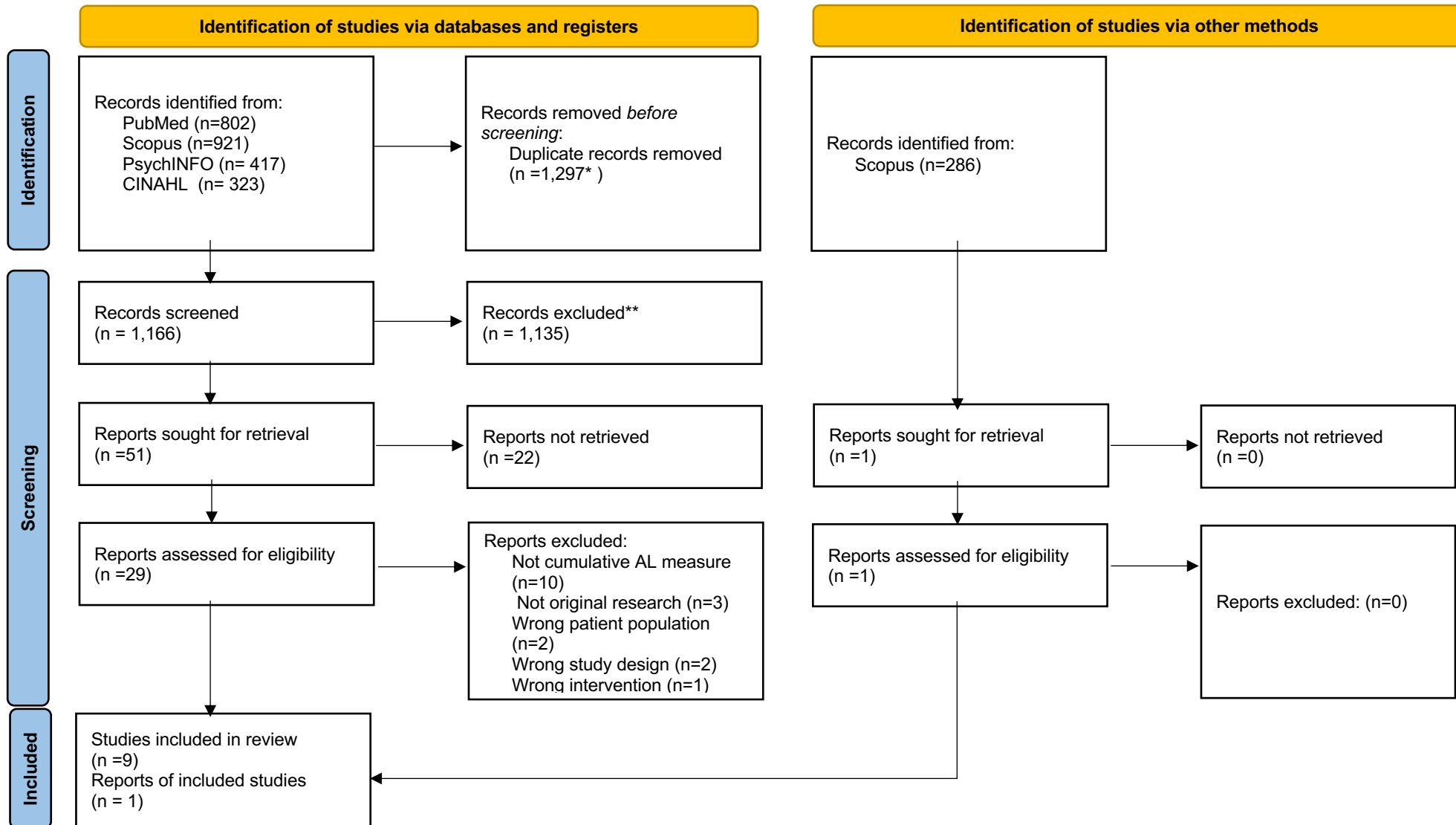
Strategic future studies are critical to understanding how AL is associated with perinatal health outcomes. Future studies can examine how AL may or may not change across the perinatal period. Such questions can benefit from understanding how to assemble an appropriate AL index across the perinatal period. Additionally, future research can explore study designs (e.g., longitudinal studies) and use clinically relevant data to facilitate decisions regarding usability and interventions that address AL in clinical care.

Conclusions

Our scoping review results provide helpful information for measuring AL in pregnancy. We learned that certain biomarkers are more commonly used in indices measuring AL during pregnancy. However, the significant heterogeneity in the number and type of biomarkers used

remains across the studies we reviewed. Consultation with perinatal professionals also yielded some interesting findings. They suggested measuring the majority of AL biomarkers in early pregnancy as indicated in the scoping review. They also provided guidance on the anticipated limitations of using an AL index in current clinical practice. They discussed that outside of blood pressure, BMI and the Glucose tolerance screen, the majority of biomarkers used in most AL indices may not be easily captured during pregnancy care. Further research is needed to explore how AL may change across the perinatal period, what combination of biomarkers would be most available in clinical data for pregnant individuals, and how this may inform its potential for clinical utility.

Figure 1.1: PRISMA Flow Diagram



*Two Studies were duplicates and removed manually, while others were removed by Covidence software.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

Table 1.1: Scoping Review Questions and Sub Questions

MAIN SCOPING REVIEW QUESTION	SUB QUESTION
1. How is AL assessed among pregnant individuals?	What data sources are used to assess relationships between AL and relevant outcomes?
	Which biological systems are considered in the measurement of AL in pregnancy?
	What biomarkers are commonly used in AL indices?
	When in pregnancy were the studied biomarkers measured, and why?
	How are AL indices quantified?
2. What physical and health outcomes/indicators have been examined with AL when researching pregnant individuals?	What obstetric health outcomes are associated with AL in pregnancy?
3. Are there any comparisons between pregnant and nonpregnant populations?	
4. How does AL research in pregnant populations examine racial/ethnic differences?	

Table 1.2 – Characteristics of Studies Measuring AL in Pregnancy

<i>Name of First Author</i>	<i>Publication Year</i>	<i>Study Design</i>	<i>Total number of participants (N)</i>	<i>Gestational period biomarkers collected</i>	<i>Source for AL biomarkers</i>	<i>Relevant Findings</i>	<i>Operationalization of AL index (e.g., sum score and z-score)</i>
<i>Lueth et al.</i>	2023	Prospective cohort study	4508	1st Trimester Pregnancy (0 to 13 Weeks)	Stored urine or serum samples collected during nuMoM2b study index pregnancy	<ul style="list-style-type: none"> After adjusting for relevant confounders, AL was associated with cardiovascular disease risk, hypertension, and metabolic disorders. 	Composite summary score of individual biomarkers collected.
<i>Wallace & Harville</i>	2013	Cross-sectional study	123	2nd Trimester Pregnancy (14 to 26 Weeks); 3rd Trimester Pregnancy (> 27 weeks)	Blood sample at 26-28 weeks Glucose tolerance test	<ul style="list-style-type: none"> There is no racial difference in the effect of allostatic load on birth outcomes 	A composite sum of z-scores for the individual biomarkers collected.
<i>Morrison et al.</i>	2013	Cross-sectional study	1138	Not Reported/Unknown	NHANES* MEC* exam data	<ul style="list-style-type: none"> Mean level of each AL-related biomarker differed significantly between pregnant and nonpregnant women 	Composite summary score of individual biomarkers collected.
<i>Hux & Roberts</i>	2015	Case-control study	113	1st Trimester Pregnancy (0 to 13 Weeks); 2nd Trimester Pregnancy (14 to 26 Weeks)	Data and plasma samples collected in the Prenatal Exposures and Preeclampsia Prevention (PEPP) Study	<ul style="list-style-type: none"> Early pregnancy AL was positively associated with higher odds of preeclampsia 	Composite summary score of 3 biological systems (i.e., cardiovascular, metabolic/anthropometric, inflammatory)
<i>McKee et al.</i>	2017	Prospective cohort study	181	2nd Trimester Pregnancy (14 to 26 Weeks)	Blood spot sample	<ul style="list-style-type: none"> Cumulative physiological dysfunction is not significantly associated with birthweight or gestational age 	Composite summary score of individual biomarkers collected.
<i>Hux et al.</i>	2017	Prospective cohort study	103	1st Trimester Pregnancy (0 to 13 Weeks); 2nd Trimester Pregnancy (14 to 26 Weeks)	Fasting blood and plasma samples at ~12,16 and 20 weeks gestation	<ul style="list-style-type: none"> AL was positively correlated with the PSQIS*, but there were no significant associations of AL with age, income, RPDQ*, the PSS*, or depression symptoms 	Composite summary score of individual biomarkers collected.
<i>Li, et al.</i>	2020	Cross-sectional study	1056	1st Trimester Pregnancy (0 to 13 Weeks); 2nd Trimester Pregnancy (14 to 26 Weeks); 3rd Trimester Pregnancy (> 27 weeks)	NHANES MEC exam data	<ul style="list-style-type: none"> Differences in levels of each AL indicator at different gestational months except for CRP* Gestion-specific AL remained steady and was comparable to nonpregnant women. AL index was valid with stress 	Composite summary score of individual biomarkers collected.
<i>Jack-Roberts et al.</i>	2020	Case-control study	62	2nd Trimester Pregnancy (14 to 26 Weeks); 3rd Trimester Pregnancy (> 27 weeks)	Fasting blood and plasma samples	<ul style="list-style-type: none"> Maternal AL was elevated in women with gestational diabetes mellitus and associated with fetal cord blood AL index. 	Composite summary score of individual biomarkers collected.

<i>Gyllenhammer et al.</i>	2022	Prospective cohort study	30	1st Trimester Pregnancy (0 to 13 Weeks); 2nd Trimester Pregnancy (14 to 26 Weeks); 3rd Trimester Pregnancy (> 27 weeks)	Blood and saliva samples	<ul style="list-style-type: none"> Maternal allostatic load is positively associated with mitochondrial enzymatic activity but was not associated with the energy production capacity of mitochondria. 	Composite summary score of standardized Gestation specific z-scores for each biomarker.
<i>Lueth et al.</i>	2022	Prospective cohort study	4266	1st Trimester Pregnancy (0 to 13 Weeks); 2nd Trimester Pregnancy (14 to 26 Weeks)	Samples from Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be.	<ul style="list-style-type: none"> High AL during early pregnancy was associated with 50% greater odds for adverse pregnancy outcomes compared with low AL. This association was most pronounced with Hypertensive diseases of pregnancy. The components of AL most strongly associated with adverse pregnancy outcomes were BMI, SBP, DBP, Triglycerides, insulin, and high-sensitivity C-reactive protein. 	Composite summary score of individual biomarkers collected.

Table 1.3: Specific Biomarkers used in Previous AL indices in pregnant individuals

Biomarkers	Biological System	Gyllenhammer et al, 2022	Hux & Roberts, 2015	Jack-Roberts et al, 2020	Hux et al., 2017	Li et al., 2020	Lueth et al., 2022	Mckee et al., 2017	Morrison et al., 2013	Wallace & Harville, 2013	Lueth et al., 2023	Total studies that used the biomarker
Systolic Blood Pressure (SBP)	Cardiovascular	X	X	X	X	X	X	X	X	X	X	10
Diastolic Blood Pressure	Cardiovascular	X	X	X	X	X	X	X	X		X	9
Total Cholesterol (TC)	Cardiovascular		X		X	X	X	X	X	X	X	7
High-density lipoprotein (HDL)	Cardiovascular		X	X	X	X	X		X		X	7
Pulse	Cardiovascular		X		X	X			X			4
Leptin	Inflammatory			X								1
tumor necrosis factor-alpha (TNF-a)	Inflammatory				X							1
C-reactive Protein (CRP)	Inflammatory	X	X			X	X	X	X		X	7
Interleukin-6 (IL-6)	Inflammatory	X	X	X	X			X				5
Triglycerides	Metabolic		X	X	X	X	X				X	6
Glucose	Metabolic			X		X	X	X			X	5
Albumin	Metabolic						X	X	X		X	4
Low-density lipoprotein (LDL)	Metabolic			X			X				X	3
Glycated hemoglobin (HbA1c)	Metabolic					X			X	X		3
Creatinine	Metabolic						X		X		X	3
Free Fatty Acids (FFA)	Metabolic	X		X								2
homeostatic model for insulin resistance (HOMA-IR)	Metabolic	X										1
Homocysteine	Metabolic								X			1
Insulin	Metabolic						X				X	2
Body Mass Index (BMI)	Metabolic/ Anthropometric	X	X		X	X	X	X			X	7

Cortisol	Neuroendocrine	X		X						X		4
Dehydroepiandrosterone-sulfate (DHEA-S)	Neuroendocrine									X		1
Total # of biomarkers specified	N/A	8	9	10	9	10	12	8	10	5	12	N/A

Table 1.4- Operationalization of AL Biomarkers

Name of First Author, Year of Publication	Total # of Biomarkers	Operationalization of biomarkers and AL indices	Account for Gestational Age	Rationale for Operationalization	Rationale for biomarker inclusion	Exclusion of Biomarkers
Wallace & Harville, 2013	5	Individual biomarkers were standardized relative to their distribution in the total sample. The AL index for each woman was then computed by summing z-scores for all five biomarkers	N/A	The z-score method allows the weight to vary with the deviation of each biomarker from the sample mean. provides flexibility given the inherently altered physiological state of pregnancy.	Previous literature	N/A
Morrison et al., 2023	10	Cutoffs were based on the distribution of each biomarker in the sample of pregnant women. The sum score of individual biomarkers	N/A	N/A	Availability within the data source	N/A
Hux & Roberts, 2015 ; Hux et al, 2017	9	NHANES 75th or 25th (HDL only) percentiles for women who have positive urine tests and were pregnant between 1-3 months (1999-2006 datasets). The sum of system domains	Yes (used early pregnancy AL). Authors hypothesized that Early pregnancy AL would best mirror pre-pregnancy values and cumulative stress	N/A	Availability within the data source	N/A
McKee et al., 2017	12	Individuals were classified as having an elevated risk of physiological dysfunction according to the quartile of each of the biomarkers. According to the literature's convention, cutoffs were established at the 75 th percentile of the population distribution. A point was assigned to each individual's score for each component that exceeded the threshold cut point.	N/A		Selected biomarkers based on previous use in literature and their impact on gestation	Yes (waist hip-ratio and glycosylated hemoglobin (HbA1c) replaced with BMI and glucose tolerance test)
Li, et al., 2020	10	The authors calculated the risk quartile for each physiological indicator based on the distribution within each of the subsamples (n=9) in which participants were at the same gestational month. The	yes (each month for each biomarker). Authors expected each physiological indicator to change over pregnancy	N/A	Availability within the data source	Yes (i.e., epinephrine, norepinephrine, and cortisol). These were not available in NHANES

		<p>gestational-month-specific ALI was also dichotomized, with values at or above the 75th percentile considered high risk for poor health and scored as “1” while values below the 75th percentile scored as “0”</p> <p>An AL index score without taking gestational month into account (non-gestational-month-specific AL score) was also calculated.</p>				
Jack-Roberts et al., 2020	10	<p>Clinical cutoffs for blood pressure (SBP \geq 120 mm Hg and DBP \geq 80mm Hg, Lower quartiles for HDL; all other biomarkers used the highest quartile value as the cutoff for High-Risk. sum score of individual biomarkers (0-10)</p>	N/A	N/A	AL biomarkers were considered as most relevant based on the literature	N/A
Gyllenhamer, et al., 2022	8	<p>Before computing the AL values, each biomarker was standardized to each stage of gestation (i.e., z-score) and then averaged across pregnancy (except pre-pregnancy BMI). An allostatic load index for each woman was then computed as the sum of z-scores.</p>	N/A	Consistent with previous Pregnancy research (Wallace& Harville, 2013)	<p>1) They are responsive to chronic maternal stress; 2) They are known to play obligatory roles in the initiation, maintenance, and progression of gestation, fetal development, and birth; and 3) They mediate the effects of the stress response and its impacts on fetal development.</p>	N/A
Lueth et al., 2022; Lueth et al., 2023	12	<p>A high AL score was defined as each biomarker's "worst" quartile, lowest for HDL and Albumin and highest for the rest. For each biomarker, values considered high risk received a value score of 1, and those not high risk</p>	N/A	Similar to prior literature.	The authors used the National Health and Nutrition Examination Survey (NHANES)	N/A

		<p>(values not in the worst quartile) were characterized as low risk and given a value score of 0. Scores for each biomarker were summed to compute an index ranging from 0 to 12</p>			<p>definition of allostatic load and the commonly used risk biomarkers focused on health disparities. These biomarkers contribute to or indicate organ and tissue damage for systems impacted (cardiovascular, inflammatory, and metabolic).</p>	
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Table 1.5: Candidate Biomarkers for an AL index for pregnancy

<i>Biomarkers</i>	<i>Systems Impacted</i>
<i>Body Mass Index (BMI)</i>	Anthropometric/metabolic
<i>Systolic Blood Pressure(SBP)</i>	cardiovascular
<i>Diastolic Blood Pressure</i>	cardiovascular
<i>Total Cholesterol (TC)</i>	cardiovascular
<i>High-density lipoprotein (HDL)</i>	cardiovascular
<i>C-reactive Protein (CRP)</i>	Inflammatory
<i>Interleukin-6 (IL-6)</i>	inflammatory
<i>Creatinine</i>	metabolic
<i>Triglycerides</i>	metabolic
<i>Low-density lipoprotein (LDL)</i>	metabolic
<i>Glucose (OR Glucose tolerance test)</i>	metabolic
<i>Glycosylated hemoglobin (HbA1c)</i>	metabolic
<i>Albumin</i>	metabolic
<i>Cortisol</i>	neuroendocrine

CHAPTER III

EXAMINE THE FEASIBILITY OF USING INDICATORS OF AN AL INDEX IN A SAMPLE OF PERINATAL INDIVIDUALS ACCESSING ROUTINE CLINICAL CARE

ABSTRACT

Introduction: Allostatic load (AL) is a theoretical concept that aims to assess how exposure to chronic stress impacts health inequities in the morbidity and mortality of perinatal individuals. However, current AL research has overlooked the potential to leverage biomarkers that are readily available through routine perinatal care. Instead, most research focus largely on broader measures that be less clinically accessible. This study aimed to explore the feasibility of using indicators of an AL index in a sample of perinatal individuals accessing routine clinical care in a large healthcare system.

Methods: We obtained a retrospective review of clinical data from a large healthcare system. We identified pregnant individuals who gave birth at UMass Memorial Health between January 1, 2018, and January 31, 2020. We also included perinatal individuals who received prenatal or postpartum care at UMass Memorial Health. We used an AL index of 11 biomarkers (i.e., SBP, DBP, BMI, Creatinine, Albumin, HbA1c, Leptin, Triglycerides, the 1-hour glucose tolerance screen, homocysteine, and DHEA-S) that were obtained from laboratory results, vitals and other diagnostic measures in the clinical data. We examined demographic variables and the frequency of available biomarkers.

Results: We identified 5,270 unique individuals who gave live birth and received their perinatal care within the study period. Of these, 96.7% had at least one indicated prenatal appointment. We also observed that the most common biomarker combination (28.9%) included SBP, DBP, BMI, a 1-hour glucose tolerance screen, Creatinine, and Albumin.

Conclusion: Some of the biomarkers that have been commonly used in previous AL indices are available in data collected during routine perinatal care, while others are not widely accessible.

This limitation highlights a need for a refined measure that leverages biomarkers that are routinely collected in perinatal care to enhance the feasibility and clinical reference of the measure. Future studies should examine AL indicators in a sample of individuals with high-risk pregnancies, to expand the range of available biomarkers that can refine AL indices.

INTRODUCTION

Allostatic load (AL) is a theoretical concept that can aid in understanding the cumulative impacts of chemical and non-chemical stressors that result in chronic morbidity and mortality (47, 83-85). Variables that impact health outcomes include age, behavioral risk factors (e.g., diet, substance use, physical activity), genetic heredity, and physical environmental stressors (e.g., neighborhood socioeconomic deprivation, exposure to pollutants, noise). However, determinants of morbidity and mortality also include structural and social barriers and policies that impact daily living, overall health, and wellbeing (86). AL aims to assess the impact of the stress response and how the complexities of stress exposure lead to poor health.

Elevated AL is associated with adverse health outcomes in general and in clinical populations (38). Prolonged exposure to stress, or "chronic stress," is associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, as well as elevated cardiovascular, metabolic, and inflammatory system dysfunction that can be a predisposition to disease (38, 39, 52, 54, 87, 88). One such population of interest is pregnant or postpartum (perinatal) individuals. The United States has the highest rates of mortality, including those for perinatal individuals and their offspring, compared to other high-income countries, even though it spends a significant amount of money on healthcare (89).

Growing research has found that high AL in early pregnancy is associated with adverse pregnancy outcomes, including preterm birth and hypertensive disorders of pregnancy (44, 74, 90, 91). Although there is growing research to explore how socioeconomic disadvantage and structural barriers lead to health inequities through exposure to chronic stressors, there are few studies that explore the role of physiological and psychologic factors on perinatal outcomes. Such research is crucial to understanding and addressing perinatal morbidity as well as its

influence on long-term offspring health and mortality (92). When it comes to remediating racial health disparities, the growing evidence suggests that addressing AL from resulting racism and social disadvantage will be helpful (34).

AL is measured using biological markers. To generate an index, efforts to operationalize the concept of AL have used composite indices that comprise variables from several major physiological regulatory systems (e.g., cardiovascular, metabolic, immune) (47). Yet, substantial heterogeneity exists across studies as to the type and number of biomarkers considered in certain indices (59). Prior studies on AL have prospectively collected biospecimens for research purposes and assayed these specimens for specific biomarkers of interest (71, 93) or used what is available in secondary survey datasets such as the National Health and Nutrition Examination Survey to operationalize their indices. These are often limited because they do not take into account the timing of when the biomarkers were collected or reflect measures easily monitored in routine perinatal care. Medical record data has been recognized for its use in research. Unlike research where data is intentionally collected, the electronic medical record offers an extensive but unstructured repository of biomarkers and health information gathered during routine clinical care. However there is limited research on whether AL in pregnancy can be examined using retrospective medical record data. In this study, we explore the feasibility of using indicators of an AL index in a sample of perinatal individuals accessing routine clinical care in a large healthcare system.

METHODS

The study was conducted through a retrospective review of electronic medical record data (EMR) from a large healthcare system. We used EMR data from UMass Memorial Health, the largest not-for-profit healthcare system in Central Massachusetts. Our data was provided from a

data repository managed by the Research Informatics Core. The UMass Memorial Health, a clinical partner of UMass Chan Medical School, uses Epic as its comprehensive EMR, and its use extends across all its entities (including obstetrics departments at the Medical Center, Memorial campus in Worcester, MA, and the Health Alliance campus in Leominster, MA). This data repository, commonly known as the Data Lake, synthesizes data from the EMR, public health data, patient registries, and administrative data (94). The collected data is then stored and engineered to create formats for analysis. This study was approved by the Institutional Review Board at UMass Chan Medical School.

Study Sample

The data repository request specified the identification of all patients who had given birth at UMass Memorial Health pre-COVID-19 pandemic from 2018 to 2020. The COVID-19 pandemic triggered changes to clinical work and healthcare delivery, resulting in dramatic changes in clinical workflow and the use of EMR systems (95). Therefore, we only included pre-pandemic data to reduce the impact of unmeasured confounding variables on our data. Our sample included individuals who gave birth at UMass Memorial Health between January 1, 2018, and January 31, 2020, and those who received prenatal or postpartum care at UMass Memorial Health. All patients were identified using the patient ID (PATID) provided in the data.

Allostatic Load Biomarkers

In Chapter II of this dissertation, we examined and compiled a list of biomarkers that have been traditionally used in AL indices for pregnant individuals. These included biomarkers from the following systems: 1) cardiovascular (Systolic Blood Pressure (SBP), Diastolic Blood Pressure, Total Cholesterol (TC), High-density lipoprotein (HDL)), 2) metabolic (Creatinine,

Triglycerides, Low-Density Lipoprotein (LDL), the Glucose tolerance screen and Glycosylated hemoglobin (HbA1c), and Albumin), 3) inflammatory (C-reactive Protein (CRP), Leptin and Interleukin-6 (IL-6)), 4) neuroendocrine (Cortisol and Dehydroepiandrosterone Sulfate(DHEA-S), and 5) anthropometric measures (Body Mass Index (BMI)). After consultation with perinatal professionals, we identified specific labs and assessments in the data repository sample that would measure these variables in the routine care of pregnant individuals. The identification of specific labs and assessments resulted in a list of eleven candidate biomarkers for AL (i.e., SBP, DBP, BMI, Creatinine, Albumin, HbA1c, Leptin, Triglycerides, the 1-hour glucose tolerance screen, homocysteine, and DHEA-S).

Biomarkers such as Creatinine, Albumin, HbA1c, Leptin, Triglycerides, the 1-hour glucose tolerance screen, homocysteine, and DHEA-S were obtained from laboratory results that were associated with outpatient services. Component measures for SBP and DBP were assessed using all available blood pressure readings from vitals taken during prenatal or postpartum appointments. BMI values were also obtained from appointment records; however, we utilized calculated BMI instead with the limited number of height values available in the data.

Analysis

We conducted an exploratory analysis of the demographic characteristics of individuals in our study samples to explore the availability of socioeconomic variables that would be impactful in modelling the impact of AL on perinatal individuals. We also explored the availability and frequency of the AL biomarkers to see if a comprehensive AL index would be feasible to explore in this study sample. We included anyone who had at least one value for the AL biomarker of interest as a 'yes' for having that biomarker. For BMI, SBP, and DBP, there were over one hundred readings available. Upon exploring a small sample of repeated readings

(i.e., the first ten readings and the first compared to the last reading of each variable), we discovered that the first reading for each variable was the best one to use to indicate its presence. Therefore, we only included those with the first reading value as a 'yes' for these variables. Analyses include univariate and bivariate analyses of individual biomarkers. We also assessed patterns of the most available composite biomarkers for an AL index. We conducted all analyses using STATA version 18 (96).

RESULTS

After formatting the data from the Data Lake, we identified 5,270 unique individuals who gave birth and received prenatal or postpartum care at UMass Memorial Health (Figure 2.1) between January 1, 2018, and January 31, 2020. Of these, 5,094 individuals (96.7%) indicated that they had completed at least one prenatal visit (initial or routine) at UMass Memorial Health. Demographics of this sample are available in Table 2.1. Individuals in this sample could have multiple insurance payors for their care, but about 54% of individuals had a private insurance payor for their care, and about 53% had a public insurance payor for their care. Most individuals in this sample were White Non-Hispanic (50.6%), spoke English as their primary language (88.1%), were Christian (46.4%), and were either married or had a significant other (60.4%). Most deliveries were also single-baby deliveries and not delivery of twins. Out of the total 5,270 unique individuals, 47.5% (n=2,502) received their postpartum care at UMass Memorial Health, with 46.0% (n=2,423) receiving both prenatal and postpartum care at UMass Memorial Health in the study period. There were 2.5% (n=131) of the individuals who had two separate deliveries between January 1, 2018, and January 31, 2020.

Next, we examined the availability of the 11 candidate biomarkers for AL. Out of our total sample (N=5,270), about 0.1% (n=3) had at least one value for DHEA-S, and 0.2% (n=12)

had at least one value for leptin. For homocysteine, 1.1% (n=57) had at least one value, 35.8% (n=1,886) had at least one value for Triglycerides, 81.4% (n=4,291) had at least one value for creatinine, and 37.6% (n=1,981) had at least one value for HbA1C. Also 87.7% (n=4,623) had at least one value for a 1-hour glucose tolerance screen, and 65.9% (n=3,474) had at least one value for Albumin. As for vitals and other assessments, 99.96% (n=5,268) of individuals had at least a first value for blood pressure (i.e., SBP and DBP), and 97.7% (n=5,146) had the first value for BMI. Many individuals for these biomarkers had a prenatal visit at UMass Memorial Health (Table 2.2). Table 2.2 shows that most individuals had at least one value for SBP, DBP, BMI, a 1-hour glucose tolerance screen, Creatinine, and Albumin. When we examined biomarker combinations, the maximum composite number of biomarkers was nine biomarkers, and the least was one. We also found that the combination of six biomarkers was the most common at 28.9% . Out of the possible 17 combinations of a six-biomarker AL index, 22.1% of individuals had the biomarkers SBP, DBP, BMI, a 1-hour glucose tolerance screen, Creatinine, and Albumin.

DISCUSSION

We conducted an exploratory analysis of the feasibility of using indicators of an AL index in a sample of perinatal individuals accessing routine clinical care at UMass Memorial Health. Out of 11 candidate biomarkers, the most common biomarker combination included SBP, DBP, BMI, a 1-hour glucose tolerance screen, Creatinine, and Albumin. This composite index only included biomarkers that reflect the dysfunction of the metabolic and cardiovascular systems. The available data made it challenging to include biomarkers that reflect the dysregulation of the HPA axis or the inflammatory system, which are all associated with the stress response (48, 76). Therefore, this index would not be classically considered an AL index as the term is currently used. However, it could be more appropriately described as a

cardiometabolic index due to its composition. Other AL indices used in this population also do not have biomarkers that measure the primary dysregulation of the HPA-axis or the neuroendocrine system and mostly rely on the majority of their biomarkers from the secondary response of the cardiovascular and metabolic systems (43, 44, 67, 74). In the initial measure of AL, ten biomarkers were used to represent different systems: 1) neuroendocrine biomarkers (DHEA-S, epinephrine, norepinephrine, cortisol), 2) cardiovascular biomarkers (SBP, DBP, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol), and 3) metabolic biomarkers (HbA1c), waist-hip ratio (WHR)). Our results suggest that the initial composition of an AL index in early research would also not have been accurately represented by using routinely captured data for perinatal individuals (49).

The resulting analysis showed that most biomarkers in the index were available for individuals who had at least one prenatal visit before delivery. This is not surprising, as prenatal visits are an important component of a healthy pregnancy, where the health of both the pregnant individual and their offspring is regularly monitored (97, 98). As the pregnancy progresses, prenatal appointments tend to occur more regularly. Therefore, without documentation of labs and vitals during prenatal visits, it would be difficult to assess any biomarkers compromising AL in the EMR.

Our study had some strengths and challenges. To date, this is the only study we know of that has explored the feasibility of finding the indicators of an AL index in EMR data for perinatal individuals. We also utilized consultation with perinatal professionals to identify the exact lab tests that measure the biomarkers of interest. This ensured that we did not include certain lab tests that did not measure our biomarkers of interest. However, one challenge was the limited frequency of some of the biomarkers in the sample. Less than 5% of individuals had at

least one value for biomarkers such as DHEA-S, Triglycerides, and Leptin. Our consultation with perinatal professionals revealed that, in contrast to research where specific biomarkers are measured individually, biomarker variables may be ordered as part of lab panels. These lab panels are ordered when there is a clinical indication of a potential pregnancy complication or to monitor the routine health of the pregnant individual and the baby. Therefore, many AL biomarkers used in research may not be routinely captured as part of clinical care. For example, creatinine is a test that can be used to measure kidney function and cardiovascular outcomes (e.g., preeclampsia). Although chronic kidney disease is an underlying cause of preeclampsia and can be detected using routine monitoring of creatinine, current US guidelines for the care of individuals with low-risk pregnancies do not include measuring kidney function (99, 100). Another challenge is that some variables may be abundantly available and need to be operationalized to weigh them adequately. For example, vitals such as blood pressure are routinely monitored during pregnancy and have a high frequency of availability. As evidenced by our results, most of the people in the sample had at least one blood pressure reading, with up to hundreds of readings for some. Future studies should examine AL indicators in a sample of patients who were indicated as having a high-risk pregnancy. Examining a subsample of high-risk individuals may yield additional variety and a higher frequency of available biomarkers to compile a clinically usable AL index.

CONCLUSION

In conclusion, we found there are challenges and limitations related to the availability of biomarkers in routinely collected clinical data commonly used in AL indices. One major challenge is that not all systems impacted by the stress response may be represented by biomarkers available for the majority of individuals in a sample of perinatal individuals. Also,

research using biomarkers in perinatal individuals that does not include most systems impacted in the stress response may be best described as cardiometabolic indices rather than AL.

Figure 2.1: Merged Data from Data Lake

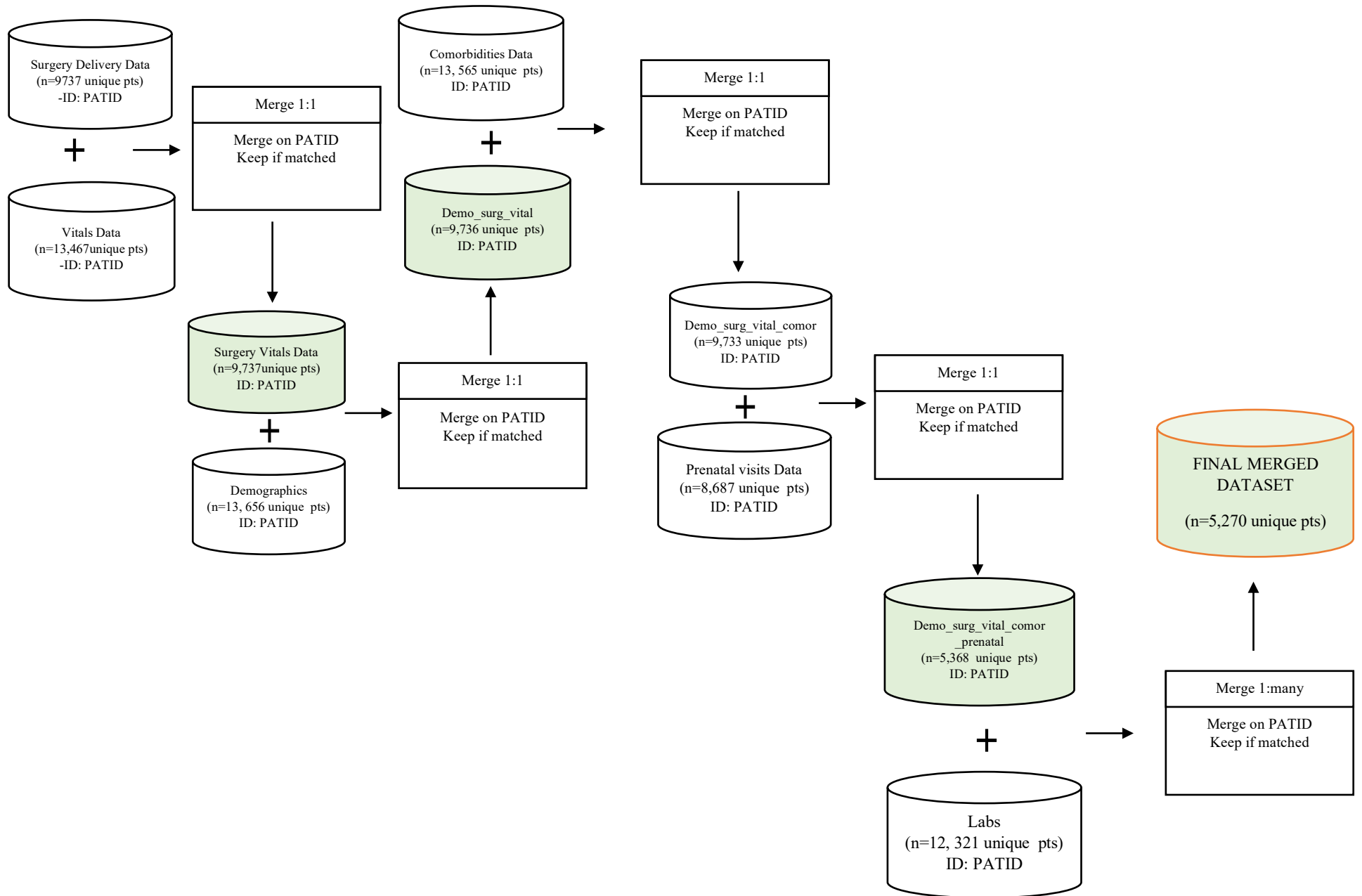


Table 2.1: Demographics in Sample (n=5,094)

DEMOGRAPHIC VARIABLE	
AGE MEAN(SD)	30.6 (5.7)
RACE & ETHNICITY N,(%)	
White Non-Hispanic/Latina/e/x	2,576 (50.6)
White Unknown Ethnicity	7 (0.1)
Black Non-Hispanic/Latina/e/x	581 (11.4)
Asian Non-Hispanic/Latina/e/x	364 (7.2)
American Indian/Alaskan Native Non-Hispanic/Latina/e/x	17 (0.3)
Native Hawaiian/Pacific Islander Non-Hispanic/Latina/e/x	1 (0.02)
Hispanic/Latina/e/x (<i>All Races</i>)	547 (10.8)
Other/Unknown Race Unknown Ethnicity	930 (18.3)
INSURANCE N,(%)*	
Public	2,691 (52.8)
Private	2,764 (54.3)
Military/Veteran	38 (0.8)
Other Payor	46 (0.9)
No Insurance	23 (0.5)
MAJOR PRIMARY LANGUAGE N,(%)**	
English	4,489 (88.1)
Spanish	318 (6.2)
Portuguese	109 (2.1)
Arabic	41 (0.8)
Vietnamese	19 (0.4)
RELIGION N,(%)***	
Christian	2,362 (46.4)
Jewish	26 (0.5)
Muslim	131 (2.6)
Buddhist	38 (0.8)
None	1,843 (36.2)
Other/Unknown	105 (2.1)
Decline To Answer	124 (2.4)
MULTIPLE DELIVERIES^A	
1	5,021 (97.1)
2	148 (2.9)
3	1 (0.02)
MARITAL STATUS,(%)	
Single ¹	1,831 (35.9)
Seperated ²	163 (3.2)
Partnered ³	3,074 (60.4)
Unknown	26 (0.5)

*Individuals have multiple payors for their care

**Other Languages have very small sample sizes

***Other religions have very small sample sizes.

^A The number of children delivered during a single pregnancy

¹ Includes Single and Widowed individuals; ²Includes divorced & legally separated individuals; ³Includes individuals who are married or have a significant other

Table 2.2: Biomarkers Available in Sample (N=5270)

<u>Biomarker^a</u>	<u>No prenatal visit</u>	<u>Prenatal Visit^b N(%)</u>	<u>p-value</u>
Systolic Blood Pressure (SBP)	174 (3.3)	5,094(96.7)	<0.001
Diastolic Blood Pressure (DBP)	174 (3.3)	5,094(96.7)	<0.001
Body Mass Index (BMI)	169 (3.3)	4,977 (96.7)	0.1
Glycated Hemoglobin (HbA1C)	51 (2.6)	1,930 (97.4)	0.02
Glucose Tolerance Test	38 (0.8)	4,585 (99.2)	<0.001
Creatinine	157 (3.7)	4,134 (96.3)	0.01
Triglycerides	34 (1.8)	1,8852 (98.2)	<0.001
Albumin	119 (3.4)	3,355(96.6)	0.6
Dehydroepiandrosterone Sulfate (DHEA-S)	0 (0)	3(100)	0.7
Homocysteine	1 (1.8)	56 (98.3)	0.5
Leptin	0 (0)	12 (100)	0.5

^a Individuals have at least one value for that biomarker and received completed prenatal care

^b Individuals with a prenatal visit have at least one appointment, which may be a new prenatal visit, initial prenatal visit, or routine prenatal visit

CHAPTER IV

ASSESS THE ASSOCIATION BETWEEN A BIOMARKER-BASED HEALTH INDEX MODELED AFTER AL, AND ADVERSE OBSTETRIC OUTCOMES AMONG RACIALIZED PERINATAL INDIVIDUALS

ABSTRACT

Introduction: Adverse obstetric outcomes, including hypertensive disorders of pregnancy, preterm birth, and depression are a public health concern, particularly for marginalized perinatal individuals. These outcomes are associated with increased long-term risks of cardiovascular disease and are driven by chronic stressors such as racism and social disadvantage. The long-term biological impact of chronic stressors can be measured using allostatic load (AL). However, AL's application in clinical practice, particularly in obstetrics, is limited due to variability in biomarker availability and the complexity of implementing standardized AL measures. This study aimed to examine the association of a biomarker-based measure, modeled after AL, among pregnant individuals who gave birth in a large healthcare system.

Methods: We analyzed data from 1,156 individuals who gave birth at UMass Memorial Health. We analyzed data from a repository of medical record information for cardiovascular and metabolic biomarkers and compiled a cardiometabolic index which included biomarkers for blood pressure, body mass index (BMI), serum Creatinine, serum Albumin, and Glucose.

Results: We found a non-statically significant 5% increase in adverse obstetric outcomes for each unit increase in the cardiometabolic index. The study sample with adverse outcomes was similar in their mean index score, age, racial-ethnic categorization and insurance classification as those individuals without adverse outcomes. The only significant finding was that partnered individuals had 27% lower odds of experiencing adverse obstetric outcomes compared to single individuals.

Conclusions: We did not find a significant association between the cardiometabolic index and the adverse outcomes or with most covariates. However, our study highlights the importance of stable social support during pregnancy. Future research will benefit from understanding the

psychosocial factors that influence perinatal outcomes and how to integrate social support into targeted interventions for pregnant individuals.

INTRODUCTION

Life-threatening complications as a direct or indirect result of pregnancy or giving birth are a significant public health concern in the US and globally (101). Adverse obstetric outcomes can foreshadow future risks of morbidity and mortality even outside of the perinatal period (102). Adverse obstetric outcomes, such as hypertensive disorders of pregnancy (e.g., preeclampsia and gestational hypertension), depression, and preterm birth are among the leading pregnancy-related complications that can be early indicators of increased risk of future diseases, such as cardiovascular disease (1-3, 9-11, 103, 104). Cardiovascular disease (CVD) is the leading cause of death in the US (103, 105). Hypertensive disorders of pregnancy are pre-pregnancy or pregnancy-associated hypertension and is associated with heart attack and stroke (106, 107). Individuals with preterm delivery, or those who gave birth to a child before 37 weeks of pregnancy, have a 61% increased risk of coronary heart disease and an 8% increased risk of stroke (108). Depression is also a risk factor and has been shown to have a bi-directional relationship with CVD (109, 110).

Racial and ethnically marginalized perinatal groups (e.g., Black, American Indian/Alaskan Native/Indigenous, and Hispanic/Latina/e/x) are among the most impacted and burdened by the heightened risk of morbidity and mortality due to these complications (111, 112). Perinatal individuals who have a historically marginalized racial or ethnic background, such as Black, American Indian, or Alaskan Native individuals, are disproportionately affected by complications such as preeclampsia and preterm birth (113-116). Even when it comes to causes of preventable death, such as mental health disorders, racial-ethnic minoritized perinatal individuals are less likely to receive screening, diagnosis, or treatment compared to their White

counterparts (117-120). Such disparities in mental health care can exacerbate adverse outcomes that impact both maternal and infant health (121-123).

Many of these perinatal health inequities are associated with adverse social and structural determinants of health, which are rooted in racism and discrimination (26, 28, 124-129). Racism and discrimination can be experienced at several levels (e.g., internalized, interpersonal, institutional, and structural). The burden of such stressors can come at physiologic and psychological costs (130). Exposure to chronic adverse stressors can lead to the wear and tear on the body and brain, known as allostatic load (AL). AL is used to quantify the cumulative burden of chronic stress on biological systems (e.g., neuroendocrine (Epinephrine), cardiovascular (Blood Pressure), metabolic (Body Mass Index), and immune (Albumin)) using a combination of biomarkers (46, 48, 49). High AL is also associated with chronic illness, negative obstetric outcomes (19, 34, 55), and higher cardiovascular-specific mortality in adults (35, 36, 72, 131). The impact of health deterioration leads to earlier onset morbidity and mortality through a phenomenon known as weathering. Weathering describes how chronic stress from social and environmental disadvantage accelerates aging and health problems, and it can be measured using AL (35).

Although it has been suggested that reducing elevated AL before, during, and after pregnancy can improve perinatal individuals' health, there are limited clinical applications of AL during the perinatal period. One reason for this limitation is the heterogeneity of biomarkers within different AL indices and the limitations of finding them within large populations (71, 132). To address this challenge in non-perinatal populations, Nobel et al. created a cardiometabolic index patterned after AL that used more commonly collected biomarkers during the routine primary care of individuals (133). However, pregnant individuals were not explicitly

examined in this research. Also, the physiological changes in response to placenta-derived and other hormones during pregnancy further limits the availability of biomarkers that may be available in the electronic medical record (41). As a result of these limitations, existing AL indices may not accurately capture physiological stress in pregnancy, potentially leading to the misclassification of individuals at high risk. This, in turn, limits the utility of AL in understanding perinatal health risks.

Our study aims to build on the research conducted by Nobel et al. and use a biomarker-based index, also patterned on AL, but one that specifically uses biomarkers that are available in clinical data from pregnant individuals. We will examine the associations of this measure with adverse obstetric outcomes. The results from this study can provide a foundation for developing methods to consistently collect and document cardiometabolic markers in the medical record during routine clinical practice. These methods may make it easier to identify and monitor those at high risk for adverse obstetric outcomes during pregnancy.

METHODS

The study was conducted through a retrospective review of electronic medical record (EMR) data from a large healthcare system's data repository. UMass Memorial Health is the most extensive healthcare system in Central Massachusetts. Our data was provided from a data repository managed by the Research Informatics Core. UMass Memorial Health uses Epic as the medical record across departments in all locations to manage the care of pregnant individuals. The Institutional Review Board at UMass Chan Medical School approved this study.

Study Sample

Inclusion in the study sample required: 1) 18 years of age and older, 2) completion of at least one prenatal visit (initial or routine) within the UMass Memorial healthcare system, and 3)

childbirth at a UMass Memorial Health location between January 1, 2018, and January 31, 2020 (N=5094). Only one pregnancy episode per unique perinatal individual was included to ensure that each pregnancy was treated as separate.

Cardiometabolic Index Measure

We developed a biomarker-based index modeled after AL, referred to as a cardiometabolic index. Component biomarkers for our cardiometabolic index were extracted from vitals and assessments during prenatal appointment visits and laboratory results. During routine office hours, initial or routine prenatal appointments occurred as face-to-face visits with a physician or an advanced practice provider (i.e., physician's assistant or a nurse practitioner) in the departments of maternal fetal medicine or obstetrics/gynecology. Following the approach Nobel et al. used to compose the Index of Cardiometabolic Health, we combined relevant biomarkers that are easily accessible in the routine care of pregnant individuals to represent the cardiovascular and metabolic systems for our index (133). Systolic Blood Pressure and Diastolic Blood Pressure were used to compute mean arterial pressure by using the formula: the sum of one-third of the Systolic Blood Pressure and two-thirds of the Diastolic Blood Pressure (133). Mean Arterial Pressure is the average arterial blood pressure through a single cardiac cycle, and its regulation involves the cardiovascular, renal, and autonomic nervous systems (134). Mean Arterial Pressure can be an alternative measure used to capture the exposure of the person to heightened pressure. It has been shown to have predictive value similar to or more than Systolic and Diastolic Blood Pressures alone in regard to hypertension and hypertensive disorders like pre-eclampsia (135, 136). For the markers that were used to measure metabolic functions, we used a 1-hour Glucose Tolerance Screen, Creatinine and Albumin laboratory values. Although the Glucose Tolerance Screen is not traditionally incorporated into metabolic indicators as

commonly as glycated hemoglobin and fasting glucose, it is more consistently measured during pregnancy (137). Therefore the 1-hour glucose tolerance test was selected as a metabolic marker in our index due to its routine and widely available use for gestational diabetes screening (138). Both Creatinine and Albumin values were from serum samples to reflect chronic system dysregulation related to metabolic health (139). We also used Body Mass Index (BMI) recorded at an initial prenatal appointment. Although the index is not robust like most AL indices, the selection of components do cover critical systems impacted by chronic stress and adaptation, particularly during pregnancy. Serum albumin strengthens the index by adding a marker of inflammation and systemic health, which are particularly relevant for the physiological adaptations of pregnancy (140). Out of our initial study population, we restricted our analytic sample to include individuals with at least one recording of the component measures in our cardiometabolic index (n=2,736). The final sample utilized for analysis was limited to those who had values present for all measures (n= 1,156).

Component biomarkers were summarized into a cardiometabolic index for each unique individual in the sample. Cutoffs were derived using the sample population (Table 3.1). Individuals in the sample were categorized as high-risk for values ≥ 75 th percentile for the biomarkers such as BMI, and mean arterial pressure except for albumin, which was categorized as "high-risk" for values below the 25th percentile cutoff. We used the count-based method to score the cardiometabolic index, where participants were categorized as having a high risk for each biomarker and were given a score of 1. In contrast, others were given a score of 0. Possible index scores ranged from 0 to 5. Similarly, we created an alternate cardiometabolic index incorporating known clinical thresholds for pregnancy or for non-pregnant adults, if clinical guidelines were not available for pregnant individuals (141-143) (Table 3.1). We kept Systolic

Blood Pressure and Diastolic Blood Pressure as separate biomarkers in the cardiometabolic index derived from clinical cutoffs, since there was no literature on a clinical cut off for Mean Arterial Pressure. Again, if individuals had the cutoff or higher, they were given a score of 1 and 0 if lower than the cutoff (except Albumin). Possible index scores ranged from 0 to 6.

Outcome Measure

The primary outcome of interest was a dichotomous composite variable identified as adverse obstetric outcomes. This composite outcome included hypertensive disorders of pregnancy, preterm birth, low birth weight, and the presence of depression symptomology. We selected these outcomes as components of the composite adverse obstetric outcome variable due to their established association with CVD risk, clinical relevance to perinatal health, prevalence, and data availability within the study population (106-110). They were chosen as factors associated with long-term cardiometabolic health risks in perinatal populations. Hypertensive disorders in pregnancy included preeclampsia and chronic and gestational hypertension (144). We used ICD-10 codes to establish the diagnosis of hypertensive disorders in pregnancy during the pregnancy episode from the patient problem list in the EMR. Preterm birth was defined as delivery of live birth before 37 weeks of pregnancy are completed and calculated using the gestational age at delivery (145). Low birthweight was defined as giving birth to a baby who was born weighing less than 2,500 grams (146). We identified any positive screening for depression symptoms available during the pregnancy episode. Depression symptoms was defined as a positive screen for depression using the Edinburgh Postnatal Depression Scale (EPDS) with a score of 10 or greater, which indicates the presence of symptoms that may need further evaluation and treatment (147). Mental health screening for perinatal individuals at UMass Memorial Health adheres to recommendations from the Alliance for Innovation on Maternal

Health Perinatal Mental Health Conditions Patient Safety Bundle (i.e., initial prenatal visit, 24-28 weeks, 6 weeks) (148, 149). All these variables were compiled into a composite adverse obstetric outcome variable, where individuals were included if they had at least one of the specified outcomes.

Covariates

Covariates considered were age (in years), insurance payor type, relationship status, and race/ethnicity. These covariates were identified based on prior literature and the relationship to chronic stress, health inequities, and adverse obstetric outcomes (150-152). Age was divided into two categories to examine the age ranges at which pregnant individuals are at risk for pregnancy-related complications. Individuals over 35 years of age are more at risk for complications, including preterm labor, gestational diabetes, and pre-eclampsia (153). Insurance payor type was categorized as public or private. In Massachusetts, pregnant individuals are eligible for MassHealth Standard coverage during their pregnancy. Even if an individual has a higher income, they may still qualify for coverage through MassHealth's Children's Medical Security Plan or the Health Connector during their pregnancy and for 12 months postpartum, regardless of immigration status (154). The only disqualifying criteria would be if they did not reside in the state of Massachusetts. Therefore, anyone without an insurance payor identified was recategorized as part of the public insurance group (n=3). Relationship status was categorized as single/unpartnered (i.e., single or widowed), separated (i.e., divorced and legally separated), and partnered (i.e., married or have a significant other). Race/ethnicity was defined as the race and ethnicity recorded in the health record (e.g., White Non-Hispanic, Black Non-Hispanic, and Hispanic of All races). Individuals whose ethnicity was unknown but whose race was documented in the EMR were categorized by race. The race/ethnicity variable was then

dichotomized to non-Hispanic/Latina/e/x White and those who were identified as being from racially and ethnically marginalized backgrounds (n=148). We did not include individuals whose race and ethnicity were identified as unknown for this variable. If race was identified as other, they were included in the minoritized group. Due to the sample size, non-Hispanic White individuals were specified as the reference group for race/ethnicity. However, this was not the ideal choice for this study, as it does not center the populations most affected by adverse obstetric outcomes or address the structural inequities contributing to the disparate risks of these outcomes.

Statistical Analysis

First, we conducted a comparative analysis of these covariates between those who were included in the final study sample versus those not included. We then examined the frequency of adverse outcomes and the demographics of the sample (e.g., age, relationship status, and insurance). We also conducted an analysis examining the frequency of the different outcomes by racial-ethnic background (Table 3.2). We performed chi-square tests to compare covariates for the categorical variables and t-tests for the normally distributed continuous variables. We then examined the rate of the adverse outcomes in our sample and the distribution of values for each biomarker by adverse outcome status (Table 3.3). We also examined crude and adjusted logistic regression models to assess the association of our index and the pertinent covariates. Our adjusted model for the association between our adverse obstetric outcomes and the cardiometabolic index included racial-ethnic status (White, Minoritized, or Unknown/Other), insurance, and relationship status as a priori confounders (150, 151). Crude and adjusted odds ratios (aOR) with 95% confidence intervals (CI) were reported. To evaluate any potential effect modification, we also tested interaction terms between the cardiometabolic index and racial-

ethnic status as well as maternal age, based on prior literature suggesting that these factors may modify the relationship (155, 156). Interaction terms for the cardiometabolic index and race/ethnicity, as well as the cardiometabolic index and maternal age, were included in logistic regression models, adjusting for relationship status and insurance. We assessed interaction terms for statistical significance and overall model improvement using likelihood ratio tests and evaluation of model fit. All analyses were conducted using STATA version 18 (157).

RESULTS

Firstly, we found that individuals included in the final study sample differed significantly from those not included with respect to maternal age ($p < 0.001$), relationship status ($p < 0.001$), and insurance payor type ($p < 0.001$), but not with respect to race and ethnic identity ($p = 0.170$). Overall, we found the rate of adverse outcomes to be 38.6% in our sample. However, there were no significant differences in the rate of adverse outcomes by racial and ethnic identity (39.5% for Non-Hispanic Whites vs. 37.9% for Minoritized individuals, p -value=0.566). Table 3.4 shows no significant differences between individuals with and without an adverse obstetric outcome regarding the mean cardiometabolic score, age, race/ethnicity, and insurance type. Relationship status and number of children delivered show a statistically significant difference (p -value=0.05), showcasing that individuals with adverse obstetric outcomes are more likely to be single and less likely to be partnered than those without an adverse obstetric outcome in our sample. The results also reveal that the majority of the sample had singleton deliveries. As shown in Table 3.4, most individuals in the study sample were younger than 35 years (79.6% with adverse outcomes vs. 80.9% without adverse outcomes). We also observed that racial and ethnic composition is similar across those with and without an adverse obstetric outcome. Also,

although not statistically significant, we observed that a slightly higher percentage of individuals without an adverse obstetric outcome have private insurance (46.3% vs. 41.9%).

Most individuals experienced one adverse obstetric outcome with perinatal depression being the most common regardless of race or ethnic identity (23.8% among White individuals and 21.9% among marginalized individuals) (Table 3.2). There were no significant differences between the percentage of individual with the various adverse obstetric outcomes across race and ethnicity. We used the model without interaction terms as the primary model for interpretation in the analysis. It retained the most observations ($n=1,140$) for each model (Tables 3.5 & 3.6) and provided the most stable and interpretable results.

In our crude model associations with adverse outcomes, most of our variables had a non-statistically significant result (Table 3.5). The results from our cardiometabolic index based on cutoffs derived from the sample show that a one-unit increase in the cardiometabolic index slightly increases the odds of adverse outcomes by 5%, but this result is not statistically significant (OR: 1.05 , CI:0.93-1.21). For individuals who were 35 years or older, we found an 8% increase in the odds of adverse outcomes compared to younger individuals (OR:1.08, CI:0.80-1.46), which was not statistically significant. The only significant finding was relationship status, where those who were partnered had reduced odds of adverse obstetric outcomes compared to those who were single (OR:0.71, CI: 0.56-0.91). When adverse obstetric outcomes and the cardiometabolic index were incorporated into a comprehensive model that adjusted for maternal age, racial and ethnic identity, insurance, and relationship status, we found that the odds of experiencing adverse obstetric outcomes still increased by 5% for each one-unit increase in the cardiometabolic index. However, this result was still not statistically significant (OR:0.1.04, CI: 0.92-1.20). There was a 12% increase in the odds of an adverse outcome in

individuals who were 35 years or older compared to younger individuals (aOR:1.12, CI: 0.82-1.52), which was also not significant statistically. There was also 14% reduced odds of adverse obstetric outcomes (OR:0.85, CI:0.66-1.11) for privately insured individuals compared to those with public insurance. The only statistically significant result in the adjusted model was the 27% decreased odds of adverse obstetric outcomes for those partnered compared to those single (aOR:0.73, CI: 0.56-0.95). These trends were similar for the index derived from clinically recommended cutoffs (Table 3.6). Although the adverse outcome odds only increased by 1% for each unit increase in the index score, for the most part using clinical cutoffs did not improve the association of our index with adverse obstetric outcomes. In our analysis, the models that were analyzing race/ethnicity and age with the cardiometabolic indices led to additional exclusions, reinforcing that they may not be the improve model fit.

DISCUSSION:

We assessed the associations of a cardiometabolic index with adverse obstetric outcomes, addressing gaps in research on the role of physiological dysregulation and allostatic load in obstetric outcomes. First, we observed that adverse obstetric outcomes were common in our sample and did not differ significantly between individuals identified as White compared to their counterparts from historically minoritized racial and ethnic backgrounds. This finding is contradictory to literature that consistently demonstrates that adverse outcomes differ between minoritized and White populations, with individuals from marginalized backgrounds being more at risk (158-161). Our findings may reflect the unique characteristics of the patient population at UMass Memorial Health. The UMass health system may provide access to prenatal care and health interventions that may mitigate disparities typically observed in adverse obstetric

outcomes. Additionally, our sample had relatively high prevalence of adverse obstetric outcomes across all racial and ethnic groups, which may have limited our ability to detect differences.

Perinatal depression was the most common adverse obstetric outcome across all racial and ethnic groups, emphasizing its significance as a universal concern. This finding highlights that perinatal depression affects individuals across diverse demographic and socioeconomic backgrounds, and that there may be shared biological, psychological, and social stressors during pregnancy and postpartum that can impact mental health across groups (162). Structural inequities may amplify these baseline risks but do not seem to diminish the widespread vulnerability to depression in the perinatal period. Therefore we need universal screening and interventions in perinatal care settings to identify those at risk and interventions to assist them with treatment and symptom resolution (163). Lastly, it is possible that the cardiometabolic index, as a measure of physical health, might be similarly linked to adverse outcomes across all groups, which could explain why the social factors assessed in our analysis had less impact in our findings.

While several independent variables were examined, most did not have a statistically significant relationship with adverse obstetric outcomes, suggesting that many of the commonly considered risk factors may have a limited impact on predicting these outcomes in this population. Notably, although the cardiometabolic index integrated several key factors often linked to chronic stress and cumulative biological dysregulation, there were no significant associations with adverse obstetric outcomes in this study. Despite their relevance in clinical contexts, variables such as age of the perinatal individual, race, ethnicity, and insurance status were not significantly associated with adverse obstetric outcomes (150-152).

The most notable finding in our study was related to relationship status. Pregnant individuals with non-separated partners (i.e., married or partnered) had significantly lower odds of experiencing adverse obstetric outcomes compared to those who were single (i.e., single or widowed). Other relationship categories (separated or unknown status) did not demonstrate significant associations with the odds of adverse obstetric outcomes. This suggests that social support, particularly from a stable partner, may play a protective role during pregnancy (164, 165). Stable social relationships may reduce stress and contribute to improved obstetric outcomes (166). Also, those who are partnered may have more socioeconomic stability due to dual income. With two sources of income there are increased financial resources that can impact better housing, reduce the impact of financial setbacks, improve nutrition and enhance access to better prenatal care (167). These are socioeconomic factors that proxies like insurance may not be able to accurately reflect (168). We need further research to understand the specific elements of social and partner support that are most protective and how these can be leveraged in interventions to support pregnant individuals who lack stable partnerships.

One of the significant limitations of our findings may reflect the inherent challenges of working with medical record data (e.g., missing data, entry errors and inconsistent documentation). The limited associations between well-known risk factors with adverse obstetric outcomes, insurance status, and the high p-values for many covariates may reflect the challenges of using medical record data and the limited sample sizes. Medical record data is often subject to inconsistencies, incomplete data entry, and potential biases in capturing certain variables (169, 170). While medical record data provides a source of high-volume data, integrates real-world data, and can be cost-effective (171, 172), one distinct challenge is that data are not collected for research purposes (173). These limitations may obscure the relationships between health metrics,

like the cardiometabolic index examined in this study, and adverse outcomes, suggesting a need for more granular and standardized data collection in future research. Another limitation was the scarcity of socioeconomic data in the data source. Medical records often do not contain socioeconomic status variables such as income, education, and employment (174, 175). These variables are crucial for studying health disparities but are usually absent or found in written notes rather than structured fields (175).

Despite challenges with missing data or variability in how data is recorded across different systems, medical records provide the most feasible, scalable, and cost-effective way to study stress's biological impacts in pregnant populations retrospectively (176, 177). That is one strength of this study. Another strength is that we used the most robust sample available. By selecting the model without interaction terms, which retained more observations, we improved statistical power, greater precision in estimating associations, and enhanced model stability. We also analyzed indices with both sample-derived cutoffs and clinically established thresholds in to ensure that the findings were robust and generalizable. While the index that uses sample-derived cutoffs is more sensitively tailored to the specific population, using clinical cutoffs from established guidelines enhances the relevance for clinical practice. The consistent findings across both approaches demonstrates that the cardiometabolic index is not significantly associated with odds of adverse obstetric outcomes.

CONCLUSION:

We were unable to compile a traditionally structured AL index because most of the biomarkers were not readily available, however, we were able to examine a comprehensive cardiometabolic index within pregnant individuals giving birth at a large healthcare system. We did not observe any significant associations with any variables except when examining the association of those

with a stable partner compared to those who were single. This finding may be due in part to limitations within our data sample and the type of data source used. Future research should explore how different factors, such as relationship status and other social determinants interact with stress and contribute to an increased risk of adverse obstetric outcomes. This understanding can enhance the development of solutions and interventions to address these outcomes for perinatal individuals. Also having improved data collection methods within medical records, particularly around social determinants and commonly used biomarkers in AL indices, may enrich the research and help boost the clinical application of measures such as AL in obstetric care.

Table 3.1: Sample-Derived and Clinically Recommended Cutoffs for a Cardiometabolic Index

<u>Component</u>	<u>Mean (SD) in Sample</u>	<u>Sample-Derived Cutoff</u>	<u>Clinically Recommended Cutoff¹</u>
Mean Arterial Pressure (MAP)	88.2 (10.82)	94	N/A*
Systolic Blood Pressure	118 (14)	126 mmHg	140 mmHg
Diastolic Blood Pressure	73 (10)	80 mmHg	90 mmHg
Albumin	3.7 (0.69)	3.3 mg/dL	3.0 mg/dL
Body Mass Index (BMI)	29.7 (8.15)	33.4 mg/dL	30 kg/m ²
Creatinine	0.66 (0.20)	0.75 mg/dL	1.1 mg/dL
Glucose Tolerance Test	117.6 (28.71)	134 mg/dL	130 mg/dL

¹ These cutoffs are derived from clinical recommendations from the American College of Obstetricians and Gynecologists or established guidelines for adults.

* Not Available (N/A) means that there are no known official clinical recommendations.

Table 3.2 : Frequency of Adverse Obstetric Outcomes (n=1,148)

	White (n= 554)	Racial & Ethnic Marginalized* (n=594)	P- value
Preterm Birth N (%)	55 (9.9)	64 (10.8)	0.638
Low birthweight N (%)	40 (7.2)	60 (10.1)	0.084
Perinatal Depression N (%)	132 (23.8)	130 (21.9)	0.434
Hypertensive disorders of pregnancy N (%)	69 (12.5)	51 (8.6)	0.32
Frequency of combined Adverse Obstetric Outcomes* N (%)			
1	162 (29.2)	165 (27.8)	0.941
2	29 (7.04)	41 (6.9)	
3	16 (2.9)	18 (3.0)	
4	2 (0.4)	1 (0.2)	

* Adverse obstetric outcomes include Hypertensive disorders of pregnancy, preterm birth, low birth weight and depression symptoms across pregnancy and postpartum

Table 3.3: Cutoff Values and Distribution of Biomarkers in Study Sample (n=1,156)

Allostatic load components	Individuals with adverse obstetric outcomes ^a (n=446)		Individuals without adverse obstetric outcomes (n=710)	
	Mean Value, SD	Cutoff Value*	Mean Value, SD	Cutoff Value*
Mean Arterial Pressure (MAP)	89.4, 9.5	95.3	87.3, 12.1	92.7
Albumin	3.7, 0.7	3.3	3.7, 0.7	3.3
Body mass index (BMI)	29.7, 9.1	33.0	29.7, 7.3	33.7
Creatinine	0.68, 0.2	0.76	0.65	0.74
Glucose tolerance test	117.1, 29.3	132	117.9, 28.4	134

^aAdverse obstetric outcomes include Hypertensive disorders of pregnancy, preterm birth, low birth weight and depression symptoms across pregnancy and postpartum

*Cutoffs were derived using biomarkers with high-risk values \geq 75th percentile of population distribution except for albumin, categorized as "high-risk" for values below the 25th percentile cutoff.

Table 3.4: Study Demographics by Adverse Outcome Status (n=1,156)

	Individuals with adverse obstetric outcomes (n=446)	Individuals without adverse obstetric outcomes (n=710)	<u>P-value</u>
Cardiometabolic index Mean, SD	2.2, 0.89	2.1, 0.88	0.396
Age N (%)			
< 35 years	355 (79.6)	574 (80.9)	0.603
\geq 35 years	91 (20.4)	136 (19.2)	
Race/Ethnicity			
White	219 (49.3)	335 (47.6)	0.566
Minoritized	225 (50.7)	369 (52.4)	
Insurance N (%)**			
Public	259 (58.1)	381 (53.7)	0.142
Private	187 (41.9)	329 (46.3)	
Children Delivered N (%)			
Singleton	423 (94.8)	703 (99.0)	0.000
Twins	23 (5.2)	7 (1.0)	
Relationship Status N (%)			
Single ¹	229 (51.6)	310 (43.9)	0.021
Separated ²	21 (4.7)	28 (4.0)	
Partnered ³	194 (43.7)	368 (52.1)	

^a Adverse obstetric outcomes include Hypertensive disorders of pregnancy, preterm birth, low birth weight and depression symptoms across pregnancy and postpartum

^{*}Includes individuals who are identified as Black, Asian, American Indian or Native Alaskan, Native Hawaiian/Pacific Islander, or Other race and/or have Hispanic/Latina/e/x ethnicity. It excludes anyone whose race and ethnicity is Unknown.

^{**}Individuals have multiple payors for their care, but public and private groups include those who have payors in that category only

¹ Includes Single and Widowed individuals; ²Includes divorced & legally separated individuals; ³Includes individuals who are married or have a significant other

Table 3.5: Association between a cardiometabolic index using sample cutoffs and adverse obstetric outcomes

	Adverse Obstetric Outcomes (n=1,156)	
	Crude Odds Ratio (95% confidence interval)	Adjusted Odds ratio (95% confidence interval)
Cardiometabolic Index	1.05 (0.93-1.21)	1.05 (0.92-1.20)
Age (in years)		
< 35 years	1	1
≥ 35 years	1.08 (0.80-1.46)	1.12 (0.82-1.52)
Race/Ethnicity		
White	1	1
Minoritized	0.98 (0.74-1.29)	0.90 (0.67-1.20)
Insurance		
Public	1	1
Private	0.83 (0.66-1.06)	0.85 (0.65-1.11)
Relationship Status		
Single ¹	1	1
Separated ²	1.01 (0.56- 1.83)	0.98 (0.54-1.79)
Partnered ³	0.71 (0.56-0.91)	0.73 (0.56-0.95)

¹ Includes Single and Widowed individuals; ²Includes divorced & legally separated individuals; ³Includes individuals who are married or have a significant other

Table 3.6: Association between a cardiometabolic index using clinical cutoffs and adverse obstetric outcomes

	Adverse Obstetric Outcomes (n=1,156)	
	Crude Odds Ratio (95% confidence interval)	Adjusted Odds ratio (95% confidence interval)
Cardiometabolic Index	1.01 (.88-1.16)	1.01 (0.88-1.16)
Age (in years)		
< 35 years (ref)	1	1
≥ 35 years	1.08 (0.80-1.46)	1.12 (0.83-1.53)
Race/Ethnicity		
White	1	1
Minoritized	0.98 (0.74-1.29)	0.89 (0.67-1.20)
Insurance		
Public	1	1
Private	0.83 (0.66-1.06)	0.85 (0.65-1.11)
Relationship Status		
Single ¹	1	1
Separated ²	1.01 (0.56- 1.83)	0.98 (0.54-1.79)
Partnered ³	0.71 (0.56-0.91)	0.73 (0.56-0.95)

¹ Includes Single and Widowed individuals; ²Includes divorced & legally separated individuals; ³Includes individuals who are married or have a significant other

CHAPTER V

DISCUSSION & CONCLUSIONS

DISCUSSION

Pregnancy is a critical period where complications from adverse outcomes (e.g., hypertensive disorders and preterm birth) can be indicators of increased subsequent cardiovascular disease (CVD) risk. Developing approaches to measure the impacts of physiological stress during pregnancy have the potential to improve care for perinatal individuals and address long-term disparate health risks. Using measures such as AL to help identify critical periods of intervention can help guide the development of tools to mitigate those risks.

Therefore, we sought to develop a health index modeled after AL, which is tailored to perinatal individuals and is informed by measures collected as part of routine care during pregnancy. We first examined and synthesized existing evidence on how AL indices have been used in previous research while incorporating input from perinatal professionals. Then we explored the feasibility of extracting the AL biomarkers in routine clinical data, prioritizing those that were indicated as clinically relevant. We identified six biomarkers that were the most robust and feasible. This combination of biomarkers was not aligned with the traditional composition of AL indices and thus, we reframed them as a cardiometabolic index, patterned after AL. Finally, we evaluated the association between the cardiometabolic index and adverse obstetric outcomes.

Aim 1: Synthesis of Current Literature

Our Aim 1 findings suggested a need for an adaptable and clinically relevant health index, especially one that could identify early markers of health risks. In our scoping review, we found variability in AL indices, particularly in biomarker selection, adaptations for gestational age or differential stress exposure by race and ethnicity. These findings reveal the gaps that still need addressing in AL research and specifically within perinatal populations. The results from

our scoping review demonstrate that while AL has been extensively studied in nonpregnant populations, its application to perinatal individuals is limited and still evolving.

Our findings reinforce the importance of standardizing biomarker selection and methodology for AL indices. The current dearth of standardized biomarkers and methodologies across AL research complicates the ability to create universally applicable AL indices in both perinatal and non-perinatal populations (53, 178). Having a standardized approach to measuring AL biomarkers would improve the comparability of findings across studies and enhance the ability to draw meaningful conclusions about the relationship between AL and health outcomes. In AL research done in perinatal populations, the interplay of gestational age, variations in biomarker selection, and methodology for calculating AL scores (e.g., count-based or z-score) make it challenging to establish how AL contributes to adverse health and reinforces health inequities (56). These inconsistencies limit the generalizability of AL research findings and hinders the ability to identify causal pathways that could drive the development of helpful health interventions and monitoring tools. Developing universally applicable AL indices or tailoring standardized indices for specific populations by incorporating biomarkers relevant to specific outcomes and adjusting for confounding factors provides AL measures that researchers can confidently use across diverse samples to examine health inequities.

Aim 2: Extracting biomarkers for an AL using data from routine clinical care

In Aim 2, we found that not all commonly used biomarkers from previous AL indices were available in data collected during routine perinatal care. From the larger set of potential biomarkers identified in our scoping review, 11 biomarkers were prioritized based on their clinical relevance and availability after discussions with perinatal professionals. Of these, only

six biomarkers were available among only a subset of the sample. The identified biomarkers such as Blood Pressure, BMI, and Glucose Tolerance are established indicators in biomarker based cardiovascular risk assessments and adverse disease trajectories (179). For example, Blood Pressure is a well-documented predictor of adverse outcomes such as future CVD risk (180). Creatinine is indicative of kidney function and metabolic health, with elevated levels indicating renal impairment (46). Lower serum Albumin levels have also been indicated as a signal for systemic inflammation and nutritional deficiency (181). Albumin has also been identified as a predictor of adverse outcomes like CVD and other chronic diseases (182, 183). Only 28.9% of individuals in the sample had complete data for this combination, highlighting current limitations in clinical data collection (e.g., missing data, consistency in biomarker collection and measurement, and timing).

These findings are supported by other studies that have highlighted the difficulty of using AL as a prognostic measure in clinical care (56, 133, 184). It has been suggested that an index that is count-based and uses simple and readily available biomarkers can be effective in assessing the cumulative impact of stress across physiological systems (181, 185). However, as we discovered, clinical data does not always have all the biomarkers collected consistently for everyone in the sample (56, 133). The biomarkers used from these datasets are collected for routine clinical purposes and not research, leading to a lack of uniformity. For example, biomarkers like blood pressure may be commonly available while cortisol or other inflammatory markers may be absent. Additionally, biomarkers in clinical data are often collected at varied times for different individuals. This makes it difficult to link AL biomarkers to specific time periods in a person's life, especially in pregnancy where the trimester can significantly influence biomarker levels (56, 186). Aligning biomarkers with specific pregnancy trimesters may have the

potential to provide better understanding of how these measures reflect underlying stress or disease, identify critical periods for intervention, and improve the accuracy of health risk assessments. Finally, biomarkers may be measured with different lab equipment or methods. or (e.g., differences in laboratory methods or equipment) (184). To address this barrier, we consulted perinatal professionals to identify specific lab and vital assessment measures that are aligned with biomarkers commonly used in previous AL research. As a result, some individuals were excluded from the sample if their biomarker measurements were not comparable to the standardized definitions we created. The results of this aim uncover that data collected during obstetric clinical care does not lend itself to measuring AL because of the many biomarkers that are missing (187).

Aim 3: Examine the association with adverse obstetric outcomes

The findings from aim 3 did not demonstrate a significant association between the composed cardiometabolic health index and adverse obstetric outcomes associated with increased risk for CVD (e.g., hypertensive disorders of pregnancy, perinatal depression, preterm birth and delivery of a baby with low birthweight). While many studies have identified an association between chronic stress or elevated AL and adverse obstetric outcomes (e.g., preterm birth or low birth weight), other literature has demonstrated weak associations or mixed results (44, 71). These discrepancies stem from the variability in how AL is measured and the complexity of pregnancy-related changes to biomarkers (186). Using retrospective medical record data presented challenges with missing data, variability in biomarker collection timing, and difficulties distinguishing the cumulative and dynamic nature of stress over normal pregnancy adaptations (71, 186). These limitations have likely contributed to the inability to

detect a significant association between the index and outcomes. Thus, these findings suggest the need for further research that captures the nuances of perinatal stress and its potential links to chronic disease trajectories, while also suggesting a need for robust and prospective data collection in medical records.

The only significant finding was 27% reduced odds of experiencing adverse obstetric outcomes for individuals who had a partner compared to single individuals. Finding that stable partnerships were protective highlights the importance of considering social and relational factors in perinatal health research. Stable relationships have positive impacts such as providing a protective buffer against stress and impacting resource sharing during pregnancy (188). However, there are still avenues that need to be explored. The benefits of stable partnerships may fluctuate with the quality of the relationship, which was not assessed in this research. There is a need to further understand why stable relationships are protective and what other protective factors may exist.

Strengths and Limitations

This dissertation has several key strengths. Firstly, this research sought to adapt AL to the unique physiological context of pregnancy and began with a robust synthesis of existing literature. The scoping review set a comprehensive foundational framework to understand how to navigate research on this topic. Another strength was the inclusion of iterative feedback from perinatal professionals in the community and those that provide clinical care at UMass Memorial Health. This ensured that the research for this dissertation was not only based on a strong backing from literature but that it also included a collaborative approach grounded in expertise, clinical practicality and the necessary perspective of clinical professionals. These perinatal

professionals could also be a target audience for future interventions in clinical settings. Therefore, it was important to gain an understanding of what labs are frequently ordered in routine perinatal care. It was also critical to glean their perceptions regarding the importance of this research and the feasibility of incorporating such an index into their standard work, even without asking those questions directly. Another key strength is that the research utilized clinical data from medical records. It is important to leverage clinical data to enhance the applicability of research to everyday settings (189). This dissertation integrated insights from perinatal health literature, epidemiology, and clinical care to demonstrate an interdisciplinary approach to understanding how measures like AL may be adaptable and useful in the care of this population.

Despite these strengths, there are also limitations that warrant consideration. For example, the clinical data was provided from UMass Memorial Health system, which has limited the applicability of the research to care settings across the US. The findings may not be broadly generalizable and may require more investigation using multi-site studies and diverse care settings. Also, retrospective clinical data introduced challenges such as incomplete biomarker availability, variability in data collection timing, and limited data for social determinants of health. The inability to examine a comprehensive list of social, psychological, and environmental factors that contribute to stress and exacerbate inequities also limited the ability to interpret the findings of this research in the critical lens of root causes of disparities. These gaps impacted the study's ability to capture the dynamic nature of stress across pregnancy and generalize findings broadly to perinatal individuals rather than just those examined in the care setting.

Implications and future research

This dissertation work has raised several clinical and research implications as well as recommendations for future research needed to advance the field. First, although the current cardiometabolic index compiled and used in Aim 3 was not statistically significant in its association with adverse obstetric outcomes, it serves as a foundation for future development and refinement of other indices. The cardiometabolic index from this study provides a starting point for creating a perinatal-specific index patterned after AL. The biomarkers were prioritized based on literature and expert feedback. Future studies should aim to adjust this index with additional biomarkers or use a different scoring method to account for the unique physiological, psychosocial, and environmental factors that affect perinatal individuals. The inclusion of these factors may provide strengthened associations between a biomarker-based index patterned after AL and adverse perinatal health outcomes.

Also, there were no racial and ethnic specifications included in the composition of the cardiometabolic index examined in this research. There were no specific changes in the thresholds of each biomarker across racial and ethnic groups, to enhance the ability to use it universally for all pregnant individuals. Although our cardiometabolic index may not be applicable to all perinatal individuals, future research can explore a more comprehensive index that can be more relevant across diverse populations.

For future work, one way to broaden the scope would be through expanding the biomarker selection. Using medical records may not be sufficient to develop a comprehensive index with an expanded set of biomarkers. There may be a need for a larger dataset that incorporates more obscure biomarkers (e.g., cortisol, Dehydroepiandrosterone sulfate) not as readily available in routine clinical data. For example including data from biobanks may be helpful in this endeavor (190). Biobanks may provide biological samples and associated clinical

data that can enhance how AL is measured and enable novel biomarkers to be included in AL indices.

Prospective studies can also be used to establish robust databases that would bolster comprehensive and useful AL indices, especially for perinatal populations. Future research should establish and utilize longitudinal data, specifically examining data at preconception, pregnancy, postpartum and interconception (the time between the end of one pregnancy and the start of the next pregnancy). Prospective studies for AL research can aid in tracking exposures and outcomes that can establish better causal inference. They can also provide opportunities to examine parent-child dyads and the intergenerational impacts of AL and disease trajectories through the comprehensive data collection of socioeconomic and other relevant variables. Ensuring comprehensive data collection is especially important for marginalized groups who face a higher prevalence of many high-risk diseases. Data from prospective studies in perinatal AL research can be used 1) to understand how physical adaptations across the perinatal period interact with biomarkers and may impact the association with obstetric outcomes, 2) to identify critical periods of risk that may exist to focus on to improve perinatal health and 3) to explore how biomarker-based indices can help identify trajectories beyond pregnancy.

Our findings uncover the need for improving clinical data systems with detailed demographic information that can support the identification of within-group disparities. Stress, biomarker measures and additional associated risks can fluctuate cross gestation and postpartum (186). Therefore, it is important to identify the most critical and opportune times for intervention. It is also important to identify mediating and moderating factors that can be intervened upon. It is challenging to do that with the current limitations for clinical data. Enhanced clinical data may

help expand the ability to explore socioeconomic and additional confounding factors that may be involved in the how chronic stress impacts health outcomes in perinatal populations. .

Conclusions

The research presented in this dissertation examined the existing literature on AL and resulted in the composition of a cardiometabolic index, patterned after AL. However, the cardiometabolic index was not significantly associated with adverse obstetric outcomes that are associated with cardiovascular disease. This finding may be due to the limitations of using retrospective clinical data at one clinical setting. The results may also be due to the current lack of standardized AL indices and biomarker variability that hinder comparisons across studies. These challenges limit the ability to develop robust and comprehensive health indices and study their implications in specific populations. Therefore, we found it challenging to compose a robust health index patterned after AL or see any relevant associations with adverse perinatal health outcomes.

Future research should expand the inclusion of current biomarkers and examine how stress can be measured across the perinatal period, accounting for gestational impacts. In order to successfully explore these research avenues there should be a focus on consistent data collection for social and environmental factors in clinical datasets. Future research methods should also prioritize the integration of longitudinal and other diverse data sources, along with prospective study designs to expand the availability of biomarkers and capture relevant factors associated with the stress across the perinatal period and life course.

APPENDIX A- Search String(s)/Strategy run on January 6, 2023.

<p><u>Database:</u> PubMed/MEDLINE (802 results)</p>
<p><u>Search:</u> ("Allostasis"[Mesh] OR allostas* OR allostatic OR "weathering hypothesis" OR "psychosocial stress" OR "psychosocial stresses" OR "psychosocial stressor" OR "psychosocial stressors" OR "psycho-social stress" OR "psycho-social stresses" OR "psycho-social stressor" OR "psycho-social stressors") AND ("Pregnancy"[Mesh] OR pregnan* OR perinatal OR gestat* OR childbearing OR "child bearing")</p> <p>Sort by: Most Recent</p>
<p><u>Database:</u> Scopus/Elsevier (921 results)</p>
<p><u>Search:</u> TITLE-ABS-KEY (Allostasis OR allostas* OR allostatic OR "weathering hypothesis" OR "psychosocial stress" OR "psychosocial stresses" OR "psychosocial stressor" OR "psychosocial stressors" OR "psycho-social stress" OR "psycho-social stresses" OR "psycho-social stressor" OR "psycho-social stressors") AND TITLE-ABS-KEY (pregnan* OR perinatal OR gestat* OR childbearing OR "child bearing")</p>
<p><u>Database:</u> PsycINFO/Wolters Kluwer, 1967-December Week 4 2022 (417 results)</p>
<p><u>Search:</u> (Allostasis OR allostas* OR allostatic OR "weathering hypothesis" OR "psychosocial stress" OR "psychosocial stresses" OR "psychosocial stressor" OR "psychosocial stressors" OR "psycho-social stress" OR "psycho-social stresses" OR "psycho-social stressor" OR "psycho-social stressors") AND (pregnan* OR perinatal OR gestat* OR childbearing OR "child bearing")</p>
<p><u>Database:</u> CINAHL/EBSCOhost (323 results)</p>

Search: (Allostasis OR allostas* OR allostatic OR "weathering hypothesis" OR "psychosocial stress" OR "psychosocial stresses" OR "psychosocial stressor" OR "psychosocial stressors" OR "psycho-social stress" OR "psycho-social stresses" OR "psycho-social stressor" OR "psycho-social stressors")

AND

(pregnan* OR perinatal OR gestat* OR childbearing OR "child bearing")

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