Biocultural Interrogations of Diabetes: From Cells to Populations to Lived Experiences

By Tian Lee Walker

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Dissertation Committee:

J. Josh Snodgrass, Chair

Kirstin N. Sterner, Core Member

Maria F. Escallón, Core Member

Clare R. Evans, Institutional Representative

University of Oregon

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DISSERTATION ABSTRACT

Tian Walker

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Diabetes poses a global health crisis as a rapidly rising chronic illness that requires tight management in order to prevent both early death and debilitating complications like foot amputation and blindness. Rates of this disease are rising quickly worldwide (Ali et al., 2017). Despite continuous advances in medication and technology, still only 25% of people with diabetes are able to achieve treatment goals and prevent complications. This dissertation aims to examine cellular, population, and personal struggles that contribute to the lack of treatment success and propose paths forward for solutions while expanding our understanding of humans' relationship to chronic disease.

Included are three studies that collectively examine population level physiology of diabetes in Mexico and China and lived experiences of diabetes among people in the United States (US). I examine diabetes from a US and multinational perspective and include both individual experiential perspectives and a quantitative approach that addresses research questions informed by cellular level processes and analyzes population level patterns of biomarkers. This work draws from two datasets: a study of type 1 diabetes (T1D) in the US, which included both an online survey and interviews called the Type 1 Diabetes Empowerment Study (T1DES), and

the World Health Organization's Study on global AGEing and adult health (SAGE), which included an in-person survey and biomarker collection. The key takeaways are that inflammation has an intricate relationship with diabetes that warrants more focused monitoring and future research, multi-level modeling offers a novel approach to analyzing multimorbidity and expanding our ability to model the relationship between diabetes and inflammation, and people with T1D in the United States are using many resources to supplement their diabetes care. In many instances groups who used a resource had improved management outcomes.

This dissertation includes previously unpublished coauthored material.

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research and collect CRP among people with T1D even if our sample was small! My Oregon T1D grandmas, Pat and Gemma. Though they are no longer with us, I am grateful for the chance to hear about dealing with T1D as an octogenarian and the warmth and kindness they offered me as a young graduate student in a new place with no family around. The network of T1Ds I had the honor of meeting and working with through Diabetes Community Care Team, Mama I'm Low, Type One Run, and Ducks with Diabetes.

I would like to thank my cat Caplan, for being the best therapy cat and brightening the lives of so many people in the T1D community.

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DEDICATION

For all of the people living with diabetes (or a loved-one with diabetes) who feel like it is impossible, invisible, and infuriating. Specifically for the families that were in my life while I was in graduate school. To the T1D mamas: Jaime, Keya, S, Renee, Sylwia, Julee and Caroline.

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CHAPTER I: INTRODUCTION

Diabetes poses a global health crisis as a rapidly rising chronic illness that requires tight management in order to prevent both early death and debilitating complications like foot amputation and blindness. Rates of this disease are rising quickly worldwide (Ali et al., 2017) with particularly high rates of type 2 diabetes (T2D) among older adults (Li et al., 2025). The majority of the burden of diabetes is present in low and middle income countries (LMICs) (Cho et al., 2018). This dissertation includes three studies that collectively examine lived experiences of diabetes among people in the United States (US), and population level physiology of diabetes in Mexico and China. I examine diabetes from a US and multinational perspective and include both individual experiential perspectives and a quantitative approach that addresses research questions informed by cellular level processes and analyzes population level patterns of biomarkers. This work draws from two datasets: a study of type 1 diabetes (T1D) in the US, which included both an online survey and interviews called the Type 1 Diabetes Empowerment Study (T1DES), and the World Health Organization's Study on global AGEing and adult health (SAGE), which included an in-person survey and biomarker collection.

Defining Diabetes

Diabetes is a well-known chronic disease, but despite ample technological innovations and treatment methods for both T1D and T2D, little progress has been made finding a cure or preventing its complications and ensuing death. Despite multiple forms of rigorous treatment available globally, diabetes is still the eighth leading cause of death worldwide (The Top 10 Causes of Death, 2024) and the seventh in the United States (Baumblatt et al., 2024). It stands out among inflammatory chronic diseases because of its strong metabolic (type 2) and autoimmune (type 1) causes and seemingly simple treatment solutions (Sherr, 2022). Given that

the most deadly physiological outcome of diabetes is elevated blood glucose (BG) (Brown, 1997), and the immediacy of the energy deficit caused when food cannot be efficiently converted into adenosine triphosphate for energy, the conceptualization, characterization, and treatment of the disease revolve around BG. However, part of the reason that so many people in the world unsuccessfully treat diabetes (regardless of access to medical care and technological advances in treatment) is that while blood glucose (BG) is the deadliest and the most obvious component of diabetes, there are many other factors in both its etiology and pathophysiology that remain poorly understood, untreated, and seldom measured or studied. In a 2020 mini review, medical researchers defined diabetes as "actually a disease of starved tissues, unable to absorb glucose (and other nutrients), and not a disease of high glucose levels" (Sirhan & Piran, 2020, p. 2922). In this dissertation I examine some of these gaps in existing care and understanding of diabetes by zooming in on the relationship between inflammation and BG level among people with diabetes who have achieved treatment goals (chapter II), examining the patterns that emerge when statistical complexity allows for modeling multimorbidity and inflammation among older adult populations (chapter III), and surveying "patient" use of resources beyond their medical team (chapter IV).

A Closer Look at Diabetes Types

Distinctions in diabetes types are primarily categorizations that perhaps overemphasize differences. In a recent work describing the application of intersectionality theory Kimberlé Crenshaw (2006) critiques arguments that claim categorization is problematic because no category can accurately capture an entire group of people due to intra-group variation. Crenshaw claims that we need categories in order to capture intra-group variation and the very creation of

categories is indicative of oppression and power that must not be dismissed (A. K. W. Crenshaw, 2006).

This is an area where the biocultural study of human variation (Wiley, 2023) and intersectionality theory (K. Crenshaw, 1989) come together, as both value the ability to capture intra-group variation and fight societal inclinations to assume that socially constructed groups are homogenous. Both theoretical approaches lean on the use of categories to make intra-individual differences visible highlighting the complexity of categories and the social power dynamics embedded in the processes that create them. In the case of diabetes types, there are important functions to the types that are relevant for determining course of treatment. Once time is included in the conceptualization of diabetes the clear boundaries between the types become blurred. This is advantageous to research because it means that research done on both types can be combined for a better understanding of diabetes overall. This perspective of dissolving categories for research purposes however, does not negate the utility of the categories in the determination of course of treatment.

There are a few important differences in pathophysiological timing and progression between the types. My focus in this dissertation is on T1D in the context of the US and all diabetes in the context of World Health Organization research done in Mexico and China. When talking about all diabetes, the majority type is presumed to be Type 2 given that it has been estimated that 96% of all diabetes in the world is T2D (Ong et al., 2023). Understanding the similarities between the types is as critical as understanding the differences. Diabetes, — regardless of type — is a disease in which glucose levels exceed the normal bounds possible in a healthily operating body; over time the excess glucose damages various parts of the body due to both blood transporting

glucose where it is not meant to go (*Cardiovascular Diabetology*, 2008) and glucotoxicity developing directly from the presence of excess glucose in the blood (Kaiser et al., 2003).

Type 1 is caused by an autoimmune reaction that causes the body to destroy all of the pancreatic beta cells, and type 2 is caused by insulin-resistance, wherein the cells of the body cannot get energy because the insulin is not able to transfer sugar from blood into cells for energy. Recent literature has been emphasizing the destruction of beta cells in T2D (Wysham & Shubrook, 2020), which is at times linked to autoimmune reactions triggered by obesity (Itariu & Stulnig, 2014). Similarly, insulin resistance in T1D is an emerging area of interest in T1D research (Oza et al., 2022), both among children (Khadilkar et al., 2023) and adults (Donga et al., 2015) (see Apostolopoulou et al., 2025 for a recent review on the topic). A key difference between the two types is that people with T2D are able to synthesize at least some insulin, while people with T1D are unable to synthesize insulin after all beta cells are destroyed (Sanyaolu et al., 2023).

Beyond this one major difference, however, many of the pathophysiological disruptions occur along the same mechanistic pathways as is depicted in Figure 1: some examples include insulin production issues (Sprietsma & Schuitemaker, 1994), imbalanced metabolic functioning due to insufficient insulin (Arunagiri et al., 2019; Steiner, Park, Støy, Philipson, & Bell, 2009), and disrupted physiological balance due to overly high and low blood glucose levels (Hassounah et al., 2022; Poznyak et al., 2020). In many ways, the same pathways are affected in both types, but the timing of which systems are affected first are opposite (see Figure 1).

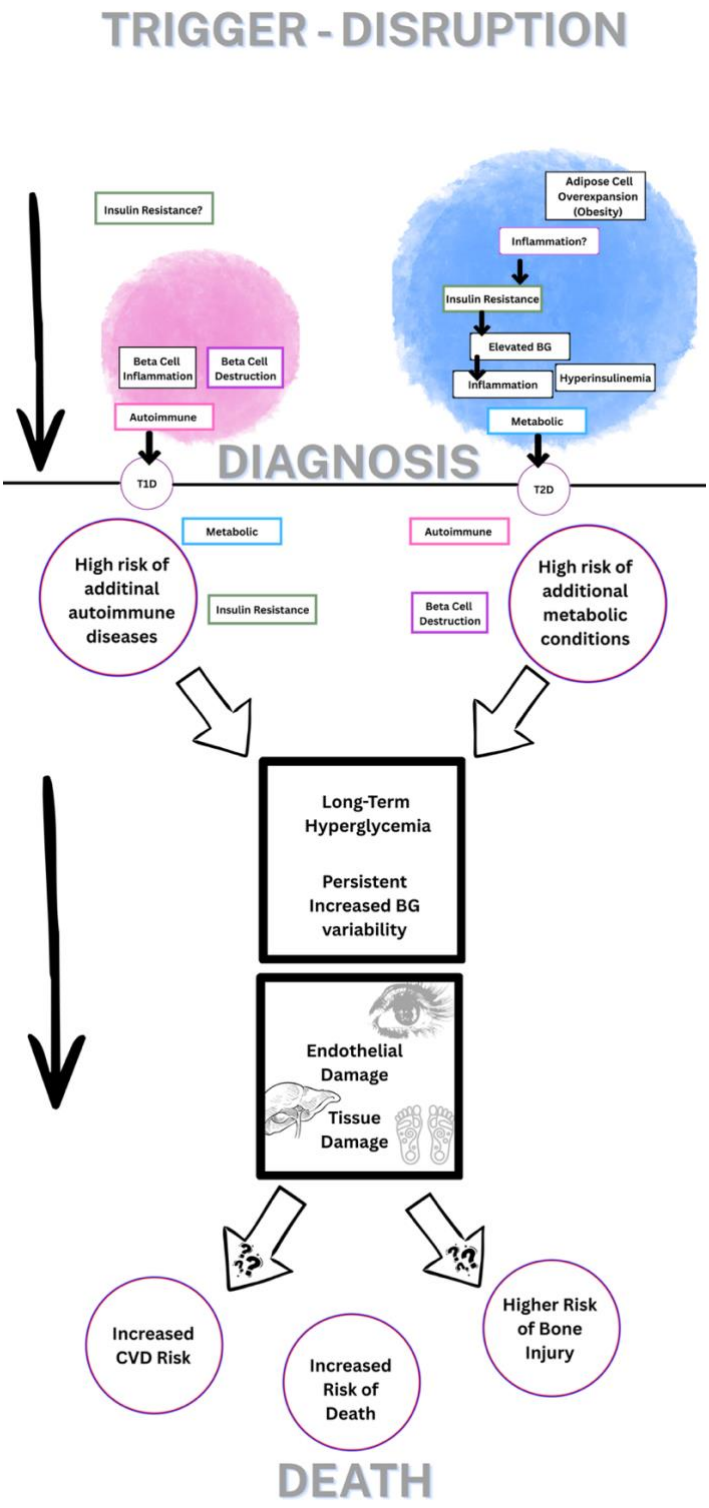


Figure 1: **Pathways and complications in T1D and T2D**, flowing from top to bottom this figure shows the ways that T1D and T2D involve similar processes at different timings and then ultimately end at the same complications with no cemented direct pathway to any one component of diabetes.

Type 1 & 2 Diabetes

As mentioned above, the majority (96%) of diabetes cases globally are type 2 (Ong et al., 2023). Symptoms can easily be overlooked until the disease starts to cause irreversible damage that leads to co-morbidities like kidney disease, neuropathy, and blindness (Khan et al., 2020). As a disease increasing rapidly across the world, there is an intense need for better detection methods, as well as preventative medical care. Inflammation, a broadly-defined cascade of chemicals released in response to physiological harm or imbalance (Oronsky et al., 2022; Rowland, 2023), plays a key role in many processes tied to diabetes, including hyperinsulinemia, insulin resistance, beta cell apoptosis and glucose variability (Barzilay et al., 2001; Cabrera, Henschel, & Hessner, 2016; Rohm, Meier, Olefsky, & Donath, 2022). Specifically, defective insulin secretion and responses that are currently associated with T2D are associated with the following inflammatory responses: lipotoxity, oxidative stress, endoplasmic reticulum stress, endocannabinoids, formation of amyloid deposits on the islets, and alterations of the gut microbiota (Donath, 2014). While underappreciated (Ritchie et al., 2017), these inflammatory responses are present in T1D as well, and thus inflammation can be linked to the development of both types of diabetes, and the concomitant initiation of dysregulated metabolic processes that lead to diabetes complications.

T1D is often neglected in research related to T2D, despite the notable overlap in pathophysiology and disease complication development (e.g., blindness, neuropathy, and kidney failure) noted above. In the case of T2D, dysregulation due to insulin malfunctioning is causal. While it is not causal in T1D, the same issues manifest because the treatment requires exogenous administering of insulin and current synthetic insulin is incapable of modeling the hormone as precisely as necessary to smoothly achieve treatment goals. Consequently, both people with T1D

and T2D struggle with insulin-related physiological functionality. There is an extensive amount of research on T2D that is relevant to T1D but has never been considered (for example: Esser, Paquot, & Scheen, 2015; Golbidi, Badran, & Laher, 2011; Mugabo, Li, & Renier, 2010; Schmidt et al., 1999). Figure 2 shows the connections between diabetes types and a couple of the key components and physiological fallouts of diabetes.

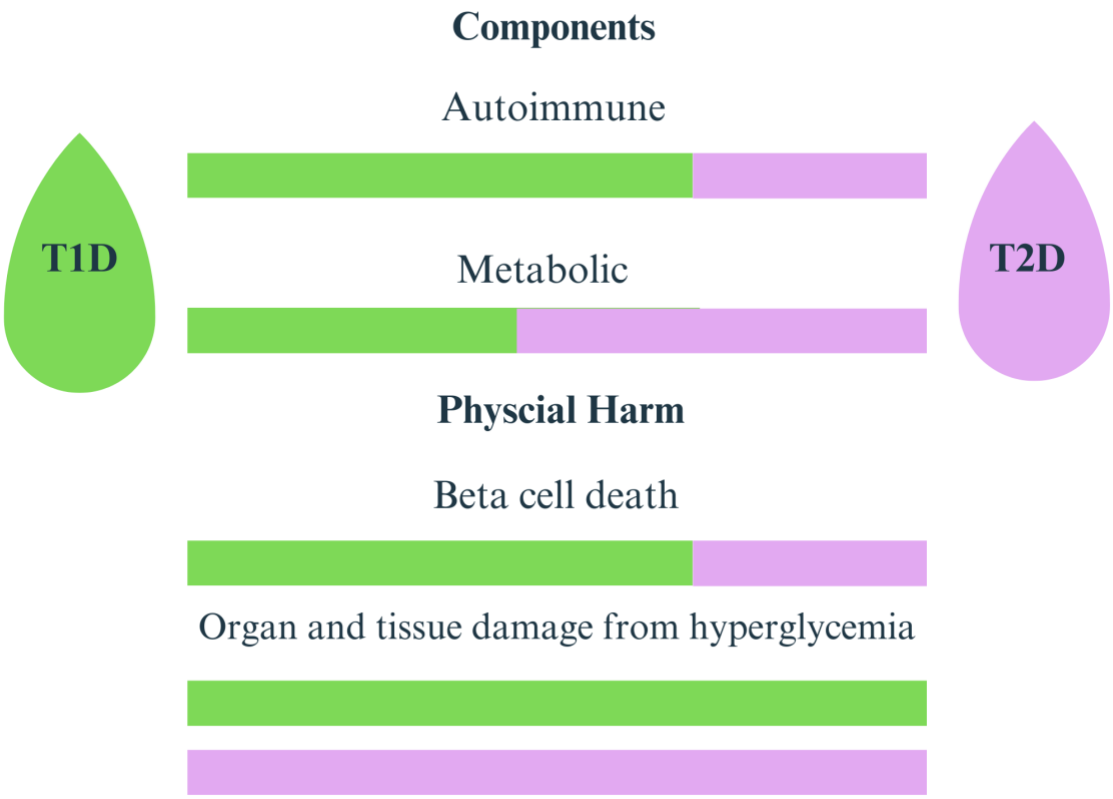


Figure 2: **Diabetes Types Continuum** Visualization of the alignment in components and physical harm between diabetes types that also depicts the difference in the significance of the role of each component and harm. While T1D is more autoimmune and T2D is more metabolic, both types require each component to develop.

Type 1 does have unique challenges due to the need for exogenous insulin. It is easier to over-treat T1D and induce hypoglycemia on a daily basis. However, T1D care would benefit immensely from applying research directed at T2D. Further evidence of these latent benefits of T2D research is that many physicians prescribe type 2 medications (e.g., Metformin, Invokana,

and Ozempic to name a few) to people with T1D off label because of the established benefits (Munir & and Davis, 2015; Scavini et al., 2019). However, the lack of control trials of T2D medicines among T1D patients gives insurance the grounds to not cover T2D medication for people with T1D.

Other Diabetes Types

Although not included in my dissertation research, there are several additional forms of diabetes that are important to consider when examining the pathophysiological pathways through which diabetes can develop. I have used evolutionary medicine theory that calls for analyzing both proximate and ultimate causes of disease to better understand how adaptive mechanisms may have shaped the development and persistence of a disease (Bateson & Laland, 2013; Nesse, 2019), to examine whether there are characteristics of diabetes that have been overlooked in current conceptualizations of the disease 4/6/2026 10:58:00 PM. It was relevant to explore all types of diabetes in order to examine the full spectrum of diabetes in humans (as well as animals). I will briefly review them here and then apply the information gained from studying these other types to discussion of type 1 and type 2. Fulminant diabetes is a form of type 1 that occurs extremely quickly (in the course of days) in adults and often does not coincide with autoimmune markers like type 1 typically does (Luo, Ma, Li, Xie, & Zhou, 2020). Viral infection, innate immunity status, adaptive immunity status, and autoimmune-associated genetic background are likely contributors to the onset of fulminant T1D, making it an autoimmune disease, but the precise pathophysiology remains elusive (Ibid). Maturity Onset Diabetes of the Young (MODY) is a group of monogenic disorders wherein a dominantly inherited beta cell malfunction manifests in people 25 and younger. Insulin is not needed as a treatment, but rather sulfonylureas (an orally consumed insulin secretagogue that increases insulin secretion via

binding to beta cells (Gieroba et al., 2025)) are often used, and depending on the location of the genetic mutation, some cases do not require medication at all (Anık, Çatlı, Abacı, & Böber, 2015). Gestational diabetes emerges during pregnancy and can continue post pregnancy as T1D or T2D; however, it often disappears after giving birth. The risk of developing T1D or T2D later in life increases for people who have had gestational diabetes (Diabetes Care & Education Specialists Association, 2020). Latent onset Autoimmune Diabetes of Adults (LADA) is a poorly understood form of diabetes that incorporates components of both type 1 and type 2 and typically occurs in people 35 years of age and older (Jones, McDonald, Shields, Hagopian, & Hattersley, 2021). Recent research found that between 4% and 12% of adults diagnosed with type 2 have LADA making it potentially equally as common as T1D (Lontchi-Yimagou et al., 2022). Lastly, just last year the International Diabetes Foundation declared a fifth type of diabetes (J. Evans, 2025) designating low insulin secretion caused by malnutrition written about by Lontchi-Yimagou et al., 2022 prior to its formal recognition as its own type. Alzheimer's Disease is sometimes referred to as type 3 diabetes, because neurons and other brain cells stop responding to insulin; however, this form of diabetes has not yet been formally recognized as an official diabetes type (Kroner, 2009). Taken together, shared characteristics of all types of diabetes are partially genetically induced insulin dysregulation in conjunction with metabolic malfunction, autoimmune destruction of beta cells or in most cases, combinations of both. All paths of dysregulation and disruption can be traced back to one of three features: insulin production/action, metabolic disfunction, and autoimmune deterioration. Each of these other diabetes types is rarer than T1D in current diagnosis rates, though LADA is likely equal to T1D and others may be more common than we know.

Beyond the Cells

Many factors that stem from social and cultural beliefs, stigmas, expectations, and systems (Mendenhall et al., 2010; Mendenhall & Weaver, 2014; Moran-Thomas, 2019; Weaver & Mendenhall, 2014) impact the experience of diabetes. Although not directly captured in the data used in this dissertation, these phenomena are ever-present in this researcher's awareness. There are clear indications that these factors are interacting with the human experience of diabetes in numerous unexplained patterns throughout this dissertation. For example, we see it in the complexity of the relationship between inflammation and diabetes and its failure to show universal trends between countries. Likewise, in the scale we chose for patient engagement, we were unable to capture the connection between viewing information about diabetes and implementing it into one's care routine. Another example of a factor affecting diabetes experiences that is not captured directly here is that diabetes is highly stigmatized. This stigma can make it difficult for people to receive the care that they need and add stress to an already challenging treatment regime. Experiences of keeping diabetes a secret came up throughout my research, and thus I want to acknowledge that diabetes is intensely difficult to navigate socially. This inevitably impacts physiology both through stress pathways, and more logistical pathways like social settings where it is impossible to take an insulin shot discretely.

Diabetes and Anthropology

The field of anthropology has discussed diabetes intensely from a cultural perspective focused on T2D including both evolutionary medicine factors contributing to its increasing rates (Gupta et al., 2024) and the struggles of daily life with T2D (Montesi, 2014; Moran-Thomas, 2019; Weaver, 2019). There has also been a substantial amount of medical anthropology

research done on improving culturally relevant medical care for people with T2D in various parts of the world (Afrin, 2019; Gammeltoft et al., 2022; Heredia-Pi et al., 2025; Little et al., 2017; Olson, 1999; Page-Reeves et al., 2013), and improving the documentation of ways that rates of T2D reflect embodied racism (Hatch, 2016; Montoya, 2011; Moran-Thomas, 2019). There is, however, a dearth of work covering T1D physiology from an anthropological perspective, and only a handful of articles that have been published in the last two decades that have focused on the cultural side of T1D (e.g., (Ferzacca, 2000, 2012; Henderson et al., 2021; Rock, 2005).

Diabetes Terminology

At times in this dissertation I will refer to "glucose" rather than "blood glucose" to be inclusive of the shift in recent years to rely on continuous glucose monitors (CGMs) for glucose measurement in all types of diabetes, but especially T1D. CGMs measure glucose in interstitial fluid through the combination of an electrochemical sensor and a calibration algorithm, and then create an estimate of blood glucose (with at times a roughly 15 minute lag) ("Calibration Algorithms for Continuous Glucose Monitoring Systems Based on Interstitial Fluid Sensing," 2024). Additionally, in line with the Association of Diabetes Care and Education Specialist's (ADCES) mission to create a culture of positive, empowering, language use in the diabetes sphere (*ADCES Speaking the Language of Diabetes*, n.d.), I refrain from using the words "good", "bad", "controlled", and "uncontrolled" to refer to diabetes management and instead use "at target" or "not at target". I make an exception and do use the word "successful" as synonymous with "at target" even though diabetes treatment should not be framed as something that someone can fail at. Additionally, although a portion of the diabetes community embraces the word "diabetic" I use "people with diabetes" or (PWD) in order to align with the ADCES position on language in diabetes care (*ADCES Speaking the Language of Diabetes*, n.d.). While

the bulk of the literature uses these terms, and to not use them can potentially create confusion, the reason for this initiative is something I observed in clinical settings as part of this dissertation work, and it is going to take more than a shift in language to undo the stigma and blame the PWD carry around with them. Therefore, shifting language is a small, doable step that I am enacting through my writing in this dissertation.

Diabetes Treatment (and its limitations)

Even with state of the art medical care, it is nearly impossible to achieve clinical treatment goals. It is worth noting that the treatment goal is still higher than people without diabetes (American Diabetes Association Professional Practice Committee for Diabetes, 2025) and thus often does not bring glucose levels back into homeostasis and completely reduce the risk of long-term complications. This is due in part to the fact that side effects of some diabetes medicines are deadly (namely insulin and drugs like sulfonylureas that increase insulin production). When we talk about diabetes management, the narrative frames management as a balance between lowering high glucose and avoiding low glucose levels. This is accurate from a management perspective but from an order of events perspective the disease diabetes induces elevated glucose, and the treatment lowers glucose. Therefore, glucose that is too low is a side-effect or overly potent effect of the treatment.

Ideal versus Reality in BG Management

Until recently, it was not possible for a person with diabetes to achieve near normal glycemia without intense risk of dying from extreme low blood glucose, and so there is limited data available on what aspects of physiology remain imbalanced in people who have diabetes, but are able to maintain blood glucose levels that mirror those of people without diabetes. This

makes it especially challenging to pinpoint additional avenues for treatment beyond the extant approach of lowering blood glucose.

Mapping Patterns

Given the large number of unknowns in physiological processes impacted by (Graves et al., 2020) and impacting diabetes (Hatch, 2016; Sanyaolu et al., 2023; Walker et al., 2014), it is critical that we triangulate the known information and map out the patterns of risk, resilience, and vulnerability. This dissertation focuses both on connections between inflammation and the main diabetes types and the strategies used by people living with T1D to obtain information needed for disease treatment. In so doing, I illustrate small pieces of the map, particularly connections between inflammation and comorbidities and between inflammation and glucose levels. This work spans from examining cellular level processes and population-level patterns, to experiences of daily life with the disease.

Diabetes and Inflammation

Inflammation has been documented as both a component of the pathophysiology of diabetes (Donath, 2014) and a downstream consequence of diabetes (Festa et al., 2002; Tilg & Moschen, 2008).While its roles are multifaceted and consequently difficult to pinpoint, inflammation likely is a key indicator of the tissue damage caused by diabetes regardless of BG levels. This dissertation examines relationships between diabetes and inflammation in an effort to provide documentation of potential benefits of increased monitoring of inflammation among all people living with diabetes (both T1D and T2D). Figure 3 indicates the possible directions of the relationships between chronic disease and inflammation.

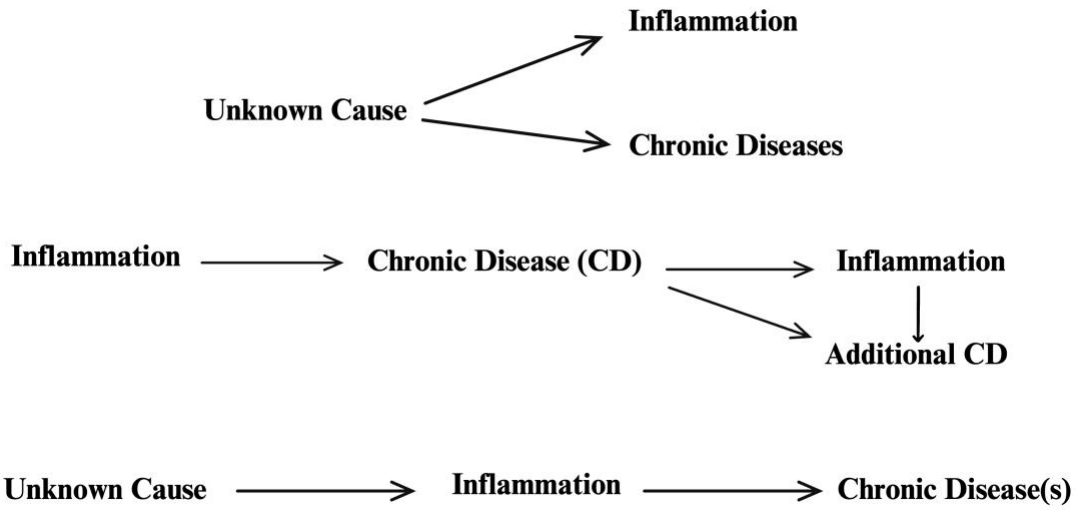


Figure 3: Potential directions of the relationships among inflammation, chronic disease, and consequent multimorbidity

Overview of Chapters

In chapter II, I examine the relationship between C-reactive protein (CRP) (a population health metric used to capture chronic low-grade inflammation) and hemoglobin A1c (HbA1c) (glycated hemoglobin that indicates average BG levels over approximately the previous 3 months) among people with and without a diabetes diagnosis in the Mexico and China datasets collected as part of the WHO's SAGE to assess whether the relationship is the same or different among the two groups (analyzing each country independently). Given that glucose level is the predominant means of tracking diabetes management outcomes, other physiological issues that manifest in people who have diabetes are often overlooked when target glucose levels are achieved. The analysis in this chapter was an effort to model statistical examination that treats people with diabetes diagnosis who are achieving near normoglycemia as their own group. While it may seem straightforward to examine whether people who have diabetes but glucose levels equivalent to someone without diabetes have elevated CRP, it is in fact more complex. The study

was done among older adults who have an average of two chronic diseases and frequently more (*Disease Burden from Non-Communicable Diseases by Age*, n.d.; Hambleton et al., 2023). The presence of higher CRP is known to be tied to chronic illness and thus, a limitation of the method in this first chapter is that it cannot account for multimorbidity. This chapter is co-authored with the following authors: Clare R. Evans, Aarón Salinas Rodríguez, Betty Soledad Manrique Espinoza, Ricardo Robledo, Salvador Villalpando, Fan Wu, Yanfei Guo, Yong Jiang, Min Yu, Xinjian Li, Yang Zheng, Jiying Xu, Alicia M. DeLouize, Nirmala Naidoo, Paul Kowal, and J. Josh Snodgrass

In Chapter III, using data from SAGE in Mexico and China, I introduce a novel statistical approach to modeling multimorbidity called Multilevel Analysis of Individual Heterogeneity and Discriminatory Accuracy (MAIHDA) that uses multi-level models to enable the evaluation of interactions between every possible combination of 4 chronic diseases and sex/gender. Visualizations of this model allow for multi-dimensional pattern detection that is not possible using traditional statistical approaches. This chapter is co-authored with the following authors: Aarón Salinas Rodríguez, Betty Soledad Manrique Espinoza, Ricardo Robledo, Salvador Villalpando, Fan Wu, Yanfei Guo, Yong Jiang, Min Yu, Xinjian Li, Yang Zheng, Jiying Xu, Alicia M. DeLouize, Nirmala Naidoo, Paul Kowal, J. Josh Snodgrass and Clare Evans.

Chapter IV, zooms in and examines health information-seeking among T1D adults in the US using the T1DES data and assesses whether engaging with various diabetes-information resources is associated with changes in mental and physical health outcomes with an emphasis on glucose outcomes. This chapter is co-authored with Sara Weston.

Theoretical orientation

The research described in this dissertation is largely informed by the expert patient experience framework (Arduser, 2017), with embodied knowledge as a driving force in disease management. I draw inspiration from Arturo Escobar's pluriverse and the possibility that the reality of a person with diabetes is in direct opposition to medical protocol and yet they exist together. I examine patient agency and activism in actions as small as making an independent decision about one's diabetes care, building on the conceptualization of models of care that follow patient initiatives.

Black Feminism and Crip Theory

Crip theory draws parallels between queer theory and critical disability studies. Through these parallels it explores ways that "compulsory able-bodiedness" is forced upon people from multiple intersecting assumptions of a desired "normal" (McRuer & Bérubé, 2006). Queer theory explores the ways diverse gender and sexuality push society to expand (Pieri, 2023), and disability studies encompasses a vast array of scholars examining how difference expands the way we think about time, existence, social roles, and life itself. All of these have had a deep influence on this work.

My work is most deeply influenced by Black feminism and biocultural theory. Physiology and culture are not as separated as the field of science would hold and so the work of Black feminists is more applicable to this biologically-focused dissertation than one might initially predict. In her famous piece on the need for tools outside of current systems, Audre Lorde (1979) states "The failure of the academic feminists to recognize difference as a crucial strength is a failure to reach beyond the first patriarchal lesson. Divide and conquer, in our world, must become define and empower" (p. 27). In the context of diabetes, defining and empowering is

done through defining the two types as thoroughly as possible and thus allowing a clear view of both the ways in which they are similar and can benefit from crosstalk between research studies. Similarly, defining the ways they are different can create the benefit of individualized models of care and unique research approaches when it comes to problem-solving disease burden.

Crip time has been relevant to me throughout the process of working on this degree. Learning that it [use the quote about exhaustion coming from seemingly nowhere, describe personal experience of the limits brought on by exhaustion, this is the it described here] had a name was extremely empowering and set me on a course to empower people living with disabilities to shed the guilt and blame for an inability to function within an expected framework of time and pace of progress.

My experience with Black Feminism really was locked in the final 10 weeks of writing this dissertation while I was also teaching an introductory course to Women Gender and Sexuality studies. The notion of "deliberate non-compliance" and this concept of an "expert patient" that defies the medically defined "compliant" behavior of a patient that follows exactly what a doctor tells them they need (because the doctor knows better than the patient because of medical school, and embodied knowledge is dismissed). There was a dramatic shift from the embrace of deliberate non-compliance, to stepping into a Black feminist framework and pushing this even further. Autonomy in one's treatment choices can be framed as an act of resistance as can the choice to seek out health information beyond what is provided by the medical team. I have come to see advocacy for self as another form of patient activism. It was new for me to frame interaction in the medical model as activism when the people doing it (including myself in the past) would not have labelled it that way.

"The Master's Tools will not Dismantle the Master's House." Audre Lorde said it best. We cannot expect change in the medical system to come from doctors. It was not until I defended this dissertation that I realized, that it is my positionality as an expert patient, one of many (like any one of my participants), that makes this work so powerful. As my committee member and fellow T1D, pointed out to me, it is my embodied knowledge that informs this work at its core. While I have found theory like evolutionary medicine to situate the questions I am asking and make them make sense for biological anthropology as a discipline, it is my embodied knowledge of the gaps in care or the schism between good blood sugar numbers and truly feeling good and living a life minimally interrupted by diabetes that informs how and why I ask the research questions that I do.

Evolutionary Medicine

The application of evolutionary medicine logic to mapping the pathways of diabetes has great potential to solve the current mysteries of unstoppable high risk for complications and co-morbidities for people with diabetes that persist regardless of treatment success. The combination of proximate and ultimate causes of physiological systems and pathways provides a clearer understanding of the weaknesses and strengths present in the body. This dissertation has used this approach and followed the clues to inflammation. The present examination of inflammation is the tiniest of demonstrations of the utility of an evolutionary medicine application to diabetes.

Chapters II and III reflect evolutionary medicine informed research questions. In the course of this dissertation work, I have aimed to explain how it is possible for T1D to persist in humans, given that it has a highly genetic component. Untreated, T1D results in death within days and commonly occurs in children. Until 100 years ago when insulin was discovered, there

was no treatment for T1D, and so how then is it possible that all of the genes contributing to T1D did not cease to exist?

There are two main paths to explore in answering this question:

1. T1D has actually never been only a childhood disease and can be triggered in years far beyond reproductive age making it possible for the genes required for T1D to occur to be passed on to the next generation.
2. There are over 100 genes involved in susceptibility to T1D (Onengut-Gumuscu et al., 2025), and thus no one gene could be weeded out through natural selection. Some reasons that this would be the case include:
    a. The genes that code for T1D also perform beneficial functions
    b. The genes that code for T1D interact with viruses in such a way that the disease can remain untriggered in a great many people and some of the critical components needed to trigger the disease state are carried in viral genomes and therefore blind to natural selection in humans.
    c. Environmental, epigenetic triggers like stress and intense amounts of sedentary behavior are needed to activate the disease

Reasons b and c led me to focus on investigating the role of inflammation. Viruses trigger inflammation as does chronic stress, sedentary behavior, and dietary factors. What if inflammation was a key to understanding diabetes and part of the processes required to turn otherwise helpful genes into the raw material for a deadly increasing rapidly around the world?

There is a large body of research on inflammation and T2D, but research on T1D and inflammation is predominantly centered on whether the beta cells become inflamed and trigger

T1D (Eizirik et al., 2009) or whether they become inflamed because of the immune-system driven destruction of these cells (Hohmeier et al., 2003). The role of inflammation leading up to autoimmune attack, as well as the role of inflammation in the pathogenesis of diabetes complications after treatment starts is rarely addressed in the literature.

My Positionality

My perspective as a woman who has lived with diabetes for 18 years informs this work. I had exposure to diabetes issues in the contexts of a clinical setting, community building both in a clinical setting and in private homes, the diabetes online community, and personal connections through a mutual aid in both Los Angeles, CA and Eugene, OR. My research questions, and my perspective as a researcher are largely informed by years of immersive work as a diabetes educator through a local non-profit pharmacy and clinic focused on helping people with diabetes who were dependent on insulin. My work reflects my own embodied experience, but also experiences from over 100 people living with diabetes who I helped to navigate insurance, access insulin, problem solve blood sugar struggles, and generate healthy coping for the constant failures and exhaustion one faces in the day to day of life with diabetes. While this dissertation focuses on cellular level understandings of diabetes, and will often talk about diabetes management, the experience of diabetes reaches into every second of waking and sleeping hours and thus goes far beyond what one might imagine when using the term “management”. It is more like throwing a lasso around the neck of a rabid giraffe: it is a pretty big target so sometimes you succeed, but it can easily kill you and often is just outright faster than you (insulin literally takes as long as 45 minutes to start working. Imagine if pain medicine took that long).

The research reported in this dissertation captures only a fraction of the anthropological work that was done in the course of my time as a graduate student. I facilitated a collaborative

research relationship between a local non-profit and another graduate student wherein we developed a 6 week-long intervention with psychological and diabetes education curriculum and biomarkers at the beginning, end, and a month post intervention. Additionally, the T1DES project included interviews focused on symptom experiences of low and high BG. These interviews informed my thinking on pathways involved in diabetes physiology but will not be directly reported on in this dissertation.

Bridge to Chapter II

In order to improve outcomes for people with diabetes, we must better understand the types of physiological issues that remain when BG has reached clinical targets. While very few people with diabetes reach these targets (~20% globally), those who do are still at greater risk of adverse outcomes like co-morbidity and early death. Thus, the ability to examine inflammation in people with at-target BG in a population level dataset where we can also compare them to other diabetes status groups creates a critical piece of information in the map to good health for people with diabetes. This is what I have done in chapter II.

CHAPTER II: BEYOND GLUCOSE LEVELS: EXAMINING WHETHER PEOPLE WITH DIABETES IN CHINA AND MEXICO WHO ACHIEVE GLYCEMIC TARGETS SHOW PATTERNS OF ELEVATED LOW-GRADE INFLAMMATION

Tian Walker, Clare R. Evans, Aarón Salinas Rodríguez, Betty Soledad Manrique Espinoza, Ricardo Robledo, Salvador Villalpando, Fan Wu, Yanfei Guo, Yong Jiang, Min Yu, Xinjian Li, Yang Zheng, Jiying Xu, Alicia M. DeLouize, Nirmala Naidoo, Paul Kowal, J. Josh Snodgrass

The WHO teams who carried out data collection included Aarón Salinas Rodríguez, Betty Soledad Manrique Espinoza, Ricardo Robledo, Salvador Villalpando, Fan Wu, Yanfei Guo, Yong Jiang, Min Yu, Xinjian Li, Yang Zheng, and Jiying Xu. The WHO administrative team included Nirmala Naidoo, Paul Kowal, and J. Josh Snodgrass. I was the primary contributor to the research design and writing. J. Josh Snodgrass and Alicia M. DeLouize provided edits, Alicia was consulted heavily during statistical test design and Clare Evans was consulted on the statistical approach.

Introduction

People who have diabetes and maintain near normalization of blood glucose remain understudied. To date there has been no systematic measurement and evaluation of inflammation levels among diabetic populations who maintain near normal glycemia or in clinical terms maintain at-target diabetes. Given the rising rates of diabetes worldwide, and the costly and debilitating complications that often follow it, there is a need for further understanding of the physiological pathways from diabetes diagnosis, microvascular and endothelial damage, macrovascular damage, glucotoxicity, and ensuing tissue damage that leads to known complications like blindness, neuropathy and nephropathy. Most critically, it is important to ascertain whether lowering of glucose levels ameliorates the harm caused by diabetes, or whether high blood glucose (BG) is simply the most deadly of many physiological changes brought on by

diabetes. Without knowing the precise pathways or what cellular processes are to blame for the initial development of diabetes nor its complications, we are left needing a proxy or parallel component of biology to capture disruptions to homeostasis. Thus, by examining inflammation levels among the diabetes populations and non-diabetes populations at varying HbA1c levels encompassing at-target diabetes (ATD) and not at target diabetes (NATD), we are able to determine whether there is reason to look more closely at inflammation levels in people with ATD or whether it is in fact the case that when glucose levels are lowered, inflammation levels decline as well and mirror the population of people who do not have diabetes.

Inflammation, C-Reactive Protein (CRP) and Diabetes

CRP is an acute-phase reactant that despite its short half-life is ever-present at elevated levels in people with chronic low-grade inflammation (Lucius, 2023). Even though the exact nature of the relationship between CRP and diabetes remains elusive, numerous studies with different foci have consistently found that they are connected (X. Wang et al., 2012). A handful of studies have concluded that CRP is likely involved in the pathogenesis of Type 2 diabetes (Festa et al., 2000; Kato et al., 2019; Olsen et al., 2025). Others have found that CRP is closely linked to diabetes but the directionality of the relationship is unclear (Festa et al., 2002; Habibi et al., 2025), and there are established connections between CRP and diabetes complications (Chen et al., 2025; Sibianu et al., 2025). Longitudinal studies focused on CRP and cardiovascular disease (CVD) have found correlations between diabetes and CRP and a pathogenic role of CRP in the development of diabetes complications (Sibianu et al., 2025).

Diabetes Is a Rising Global Concern

Premature death due to diabetes is among the most pressing of global public health issues. Diabetes causes 4.2 million deaths globally, an equivalent of one death every 8 seconds (Harding, Weber, & Shaw, 2024). The global health burden of diabetes is expanding at an alarming rate in countries of all income categories (Mohammed K. Ali, Weber, & Narayan, 2017), and prevalence is accelerating particularly fast in low to middle income countries (LMICs) with rates exceeding even the most pessimistic projections. In 2019, researchers predicted that 700 million people would be living with diabetes by 2045 (Saeedi et al., 2019). Shockingly, by 2022, 23 years prior to the projected date, the number of adults living with diabetes in the world exceeded that projection, rising to 828 million (Zhou et al., 2024). Of those 828 million, approximately 79% lived in low- and middle-income countries (LMICs) (Cho et al., 2018) which account for 80% of diabetes-related death (Lin et al., 2020).

Diabetes Treatment and Monitoring

Diabetes treatment and disease monitoring revolves exclusively around glucose levels be that through self-monitored blood glucose (SMBG), fasting glucose, Hemoglobin A1c (HbA1c, a 3-month average of blood glucose levels measured using glycated hemoglobin) or continuous glucose monitoring (CGM). It is a disease characterized by excess BG levels, which is a direct result of insulin sensitivity issues in type 2 diabetes (T2D) and a lack of insulin in type 1 diabetes (T1D). Some diabetes medications (e.g., insulin) can induce significant BG lowering (CITE), while many T2D medications increase insulin sensitivity with only mild risk of hypoglycemia. In order to meet widely accepted clinical goals for BG established by the American Diabetes Association, the International Diabetes Federation, and the World Health Organization among others, a person with diabetes must achieve an average three month BG level of 140 to154 mg/dL (equivalent to an HbA1c of 6.5-7%) or keep their blood sugar between 80 and 180 mg/dL

at least 80% of the time as measurable through a CGM (ADA, NICE, WHO). Thus, clinical diabetes treatment goals do not require for BG to be exactly the same as a person without diabetes (ranging between 80 and 120 mg/dL). This is not because there is definitive research demonstrating that there is no harm caused by slightly elevated BG, but rather it is currently not possible to achieve euglycemia without risking deadly low BG events (American Diabetes Association Professional Practice Committee for Diabetes, 2025).

A lot of the current standards of care determined by the ADA and upheld by international health agencies like the WHO, are informed by three major studies: the Diabetes Complications and Control Trial (DCCT), the Action to Control Cardiovascular Risk in Type 2 Diabetes (ACCORD) trial, and the United Kingdom Prospective Diabetes Study (UKPDS). Most information about the relationship between glucose levels and health outcomes is limited by the confines of the treatments in these studies. For example, while the goal of the Diabetes Complications and Control Trial (DCCT) was to study the difference between standard diabetes treatment at the time (in 1982) and people who keep blood sugar levels closer to levels of non-diabetics (HbA1c ~6%), the tight control group in the trial was not able to achieve the goal of 6%, consequently, there are currently no studies comparing inflammation between PWD achieving clinical goals (HbA1c < 6.5%), and people who do not have diabetes. The only data that exist show that maintaining an A1c of 7% over 11 years has extreme protective benefits in comparison to achieving an A1c of 9% since these are the averages of the two groups compared in the DCCT (1993). Interestingly, the DCCT found that maintaining lower HbA1c had protective effects in following decades even if tight control was not continued after the trial indicating that in addition to real-time physiological benefits of in-range BG, there are also long-term protective factors at play. To date, no clinical trials focused on people with diabetes have

assessed if a BG average even lower than 7% would yield further health benefits. However, research has shown that in people who do not have diabetes, increases is HbA1c are associated with greater risk of adverse health outcomes (Butalia et al., 2024).

When people who have diabetes achieve treatment goals, they still experience adverse health events like heart attacks (Vergès, 2020) and birth complications (in T1D, (Ludvigsson et al., 2019)) at higher rates than people without diabetes. We do not fully understand how the increased BG fluctuation and more time spent with extreme BG levels (glucotoxicity) affects the body. There are likely shifts in pathophysiological regulation of BG both because the levels are different and because diabetes impacts hormonal signaling needed for homeostasis. For example amylin signals satiation and when the beta cells are damaged this signal is disrupted along with insulin production. Additionally, insulin has signaling roles outside of its role to allow glucose to enter the cell that remain poorly understood (Beddows & Dodd, 2021; Kroner, 2009). There are a multitude of physiological systems that compensate for BG dysregulation (including the liver, kidney, skeletal muscles and brain) (Olsen et al., 2025). All or some of these systems' compensating actions may be contributing to the increased health risks observed in people with well-treated diabetes and it is likely that harm induced by misguided attempts to restore homeostasis would result in elevated CRP since it is an acute-phase reactant. It is probable that chronic inflammation is increasing both from glucotoxicity (from frequent sustained hyperglycemia) and tissue damage from hyperglycemic periods and simultaneously from extra-cellular compensation from these other organ systems. Therefore, we posit that at-target HbA1c in a person with diabetes does not indicate a person with a disease who has been restored to a healthy state with the assistance of medication. Instead, such a person likely has well-managed BG but will still show significantly elevated levels of C-reactive protein just as other people with

diabetes have elevated CRP levels. All people with even slightly elevated HbA1c have elevated CRP (Amanullah et al., 2010), and even at target people with diabetes have elevated HbA1c compared to people with no insulin resistance or insulin processing issues**.**

Pathways between Diabetes and Inflammation

Studies examining people with T2D with an HbA1c < 6.5% have found adverse health outcomes including increased mortality with two main explanations: 1) increased glucose variability (Ceriello et al., 2022, Nicholas, Charlton, Dregan, & Gulliford, 2013) and 2) increased hypoglycemia (Nicholas, Charlton, Dregan, & Gulliford, 2013). One proposed mechanism causing increased risk in people with diabetes and an HbA1c < 6.5% is increased chronic-inflammation levels (Vergès, 2020). This is a parsimonious explanation given that increased glucose variability (GV), hypoglycemia, and hyperglycemia induce inflammation.

Abnormal insulin sensitivity can be at play for up to 15 years before it progresses enough for a clinical diagnosis (Tsalamandris et al., 2019). We can infer inflammation and tissue damage (thus elevated CRP) likely begin prior to diagnosis alongside abnormal insulin sensitivity. CRP is likely to pick up on subtle disturbances taking place prior to a full-on disease state including tissue damage and elevated inflammation (Kushner, Rzewnicki, & Samols, 2006), making it an ideal target biomarker for a novel approach to analyzing the pathophysiology of diabetes.

A review found that glucose variability (GV) is associated with microvascular and macrovascular complications, may be associated with oxidative stress, and in critically ill, non-diabetic patients is associated with death (Siegelaar, Holleman, Hoekstra, & DeVries, 2010). Among people with diabetes (PWD) with an HbA1c < 6.5%, who take insulin or Sulphonylureas, an HbA1c in this range, can indicate an increased rate of hypoglycemic episodes

which means both that there is likely increased GV and the direct strain of hypoglycemia which is known to increase inflammation (Fisher et al., 2005). Thus, a lower HbA1c among PWD may indicate higher GV and worse health outcomes. One study found that older adults with diabetes who had an HbA1c 6.5-9% had better outcomes than people with T2D who had an HbA1c < 6.5% (Nicholas et al., 2013). However, it is important to note that it is thoroughly documented that an HbA1c within that range will result in diabetes complications like blindness, neuropathy, and amputation (DCCT/EDIC Research Group, 2024). Expanding GV to also include HbA1c variability, recent research indicates that HbA1c variability is a stronger indicator of CVD health outcomes than whether or not HbA1c is at target (Ceriello et al., 2022). We know that fluctuation beyond the narrow range of 80 to 120mg/dl of a non-diabetic increases inflammation, and thus the pathway for this finding likely includes inflammation due to high levels of GV (Howsawi & Alem, 2024).

The strong relationship between HbA1c and CRP presented in the literature holds true in studies throughout the world. In Korea (Seo & Shin, 2021a) and India (Meshram et al., 2013), studies found a positive correlation between CRP and HbA1c. Studies assessing this relationship in the United States have found this correlation as well (Barzilay et al., 2001; King, Buchanan, & Pearson, 2003). Roughly 80% of people with diabetes in LMIC's live in a state of hyperglycemia (HbA1c > 7.5%) which is known to induce chronic low-grade inflammation (Festa et al., 2000; Han et al., 2002; Stanimirovic et al., 2022; Tsalamandris et al., 2019), and incur complications including blindness, kidney failure, and limb loss. While there is still a lot unknown about all of the ways that inflammation impacts the body, there is consensus that all increases in chronic low-grade inflammation levels indicate higher risk of poor health outcomes including the development of diabetes complications.

Diabetes occurs at higher rates in older adults. Thus, older adults, a rapidly increasing demographic in LMIC's, are a demographic where these physiological issues are likely magnified, making The Study on global AGEing and adult health (SAGE) an ideal dataset to examine to better understand these relationships. In this multi-site study on chronic diseases and health in LMICs, the WHO collected nationally representative survey data and widespread biomarker data to capture disease statuses regardless of diagnosis.

Challenging HbA1c as a Stand Alone Clinically Informative Measure

Two large and widely used datasets, NHANES and UK Biobank, use diabetes diagnosis as a definitive grouping variable wherein HbA1c status does not matter for grouping once a positive diagnosis status is confirmed (D. Wang et al., 2025). However, previously published research from the WHO has grouped people based on their HbA1c regardless of their diabetes status (Dona et al., 2020), and a review on population stratification in T2D names HbA1c as one of the main stratification methods used in the literature (Hodgson et al., 2022). This grouping assumes that once people with diabetes achieve HbA1c < 6.5%, their health status is comparable to that of people without diabetes. Additionally, in T1D care settings in the US, parents report disengagement from their diabetes care team and fewer resources offered when they achieve target HbA1c for their children with T1D (Tanenbaum et al., 2024).

If elevated glucose was the only ailment present in the body of a person with diabetes, then this would theoretically be true, but there is a series of physiological disruptions that occur prior to diabetes that likely remain unresolved even when blood glucose levels are lowered. This order of events is different for type 1 and type 2 diabetes, but most likely these processes are at play in both types, just in a different order. In T2D, insulin resistance begins long before the beta

cells are so affected that they can no longer compensate (Corpeleijn et al., 2009). Blood glucose begins to be elevated in the presence of high carbohydrate intake (Campbell & Cajigal, 2001), but the body is able to compensate. In the time in between insulin resistance and compensation, physiologically harmful events occur including cellular level processes like strain on the mitochondria (Xie et al., 2008), resultant oxidative stress and the release of random oxygen species (ROS) (Luc et al., 2019; Xie et al., 2008), and then ultimately hyperinsulinemia (Thomas et al., 2019).

Each time BG is elevated these processes occur again, until the damage is beyond repair. Lowering BG buffers future deterioration of the body. However, BG lowering medication treats only one pathway to elevated BG, so prior damage and alternate pathways of harm are still likely to cause imbalance and cellular damage. Additionally, because the main measure of blood glucose levels is HbA1c which averages glucose levels over 3 months, it is possible and probable that a person with at-target HbA1c is still having events of high (and in some cases low) BG that would trigger glucotoxicity, cellular harm, tissue damage, and consequently inflammation. There is some discussion regarding the role of inflammation prior to insulin resistance (Festa et al., 2000, 2002; Tilg & Moschen, 2008), but our focus is on inflammation levels in people who already have diabetes. Inflammation is likely the first measurable malfunction beginning prior to diagnosable insulin resistance or diabetes, but not an isolated issue. It is logical that if there is more to diabetes than just HbA1c that even when A1c is brought down to ideal levels, that elevated inflammation would remain.

Questions under Consideration in our Study

The present study seeks to test if BG levels and inflammation are positively correlated across all diabetes statuses (determined by combining HbA1c levels and diagnosis status), with mean differences between each status group in two LMICs (China and Mexico). Moreover, this study also analyzes potential variation between the Mexico and China samples. To do so, we present the following hypotheses and objectives:

Objective 1: Assess the relationships between mean CRP and mean HbA1c among people of various diabetes statuses (no diabetes - HbA1c < 5.7, diabetes with HbA1c < or = 6.5%, and diabetes with HbA1c > 6.5%) in both countries.

H1: Despite at target HbA1c < 6.5%, people diagnosed with diabetes have higher CRP on average than people who do not have diabetes.

Objective 2: Assess the relationships between CRP and HbA1c continuously among people who have diabetes and those who do not in both countries.

H2: There is a significant difference in the relationship between CRP levels and HbA1c among all people with no diabetes versus all people with diabetes. We hypothesize that we will see this difference because people who have diabetes but lower HbA1c will still have elevated CRP compared to those who do not have diabetes and equal HbA1c levels.

Objective 3: Identify any universal trends between HbA1c and CRP among diabetes statuses and assess differences between the two countries.

H3: We will see the same patterns in both countries, with higher CRP correlating to HbA1c continuously across all statuses of diabetes with the expectation of highest CRP in PWD not at target, intermediate CRP in PWD at target, and then lowest CRP in people without diabetes

Methods

Hypotheses were tested using WHO Wave 1 data from of The Study on global AGEing and adult health (SAGE) collected in 2007-2010 among older adults ages 51-105 (in Mexico) and 50-96 (in China) (Kowal, Chatterji, Naidoo, Biritwum, Fan, et al., 2012). These countries represent unique middle income country populations with separate socio-economic and political histories that create vulnerability to harm from diabetes through very different paths.

Data

SAGE is a comprehensive longitudinal study of health and well-being during the ageing process in six middle income nations (Kowal, Chatterji, Naidoo, Biritwum, Fan, et al., 2012). A subset of the countries participated in different biomarker measurements. CRP and HbA1c were collected in China and Mexico. The present study uses biomarker and survey data from SAGE Wave 1 in China and Mexico to examine relationships between inflammation and glucose levels among people with different diabetes statuses.

SAGE was approved by the World Health Organization's Ethical Review Committee and each location's independent review board. All participants provided informed consent before participating (Kowal, Chatterji, Naidoo, Biritwum, Fan, et al., 2012).

A subset of people participating in the SAGE study underwent biomarker analysis in Mexico (n = 2,442) and in China (n = 6,832). Exclusions included 636 people in China and 194 people in Mexico for having an elevated CRP value that might indicate injury or acute infection, and 126 additional people in China for HbA1c levels too high for the machine to read accurately. The sample was 51.41% women in China and 60.8% women in Mexico, although in Mexico data on gender was only gathered among 1,870 of the 2,442 participants. Participant ages for this

analysis ranged from 50 to 97 years old (China: M = 62.92, SD = 9.24, Mexico: M = 68.27, SD = 9.23).

Biomarkers

The process of biomarker sampling process for HbA1c and CRP in Mexico have been explained thoroughly in a previous publication (Dona et al., 2020). In summary, standard venipuncture was used to collect venous blood in an EDTA tube. Next, these whole blood samples were homogenized and then pipetted in 20 μL aliquots onto standard Whatman 903 filter paper so that they could be analyzed using DBS procedures (Brindle, O'Connor, & Garrett, 2014; de Waal, Driver, & Warner, 2019; Lacher, Berman, Chen, & Porter, 2013; Lehmann, Delaby, Vialaret, Ducos, & Hirtz, 2013; Li & Lee, 2014; McDade et al., 2012). Analysis of the samples began after 24 hours of drying at room temperature. A 6 mm spot was punched out from the DBS card and eluted with 250 μL of PBS buffer pH = 7 for 14 hours. The Abbott Architect CI8200 chemistry analyzer for CRP was used to analyze the DBS eluates (Lacher et al., 2013). In addition, a comparison was done between the DBS measures and serum. It was analyzed using the Architect CI8200. CRP DBS values were regressed onto CRP serum controls for the comparison subsample using a Passing Bablok regression in order to create serum equivalents. The regression equation was:

CRP serum = 2.41(CRP DBS) – 1.38

Sufficient validity for analysis was indicated by a strong correlation between CRP DBS values and CRP serum values, Pearson's $r = 0.99$. To further assess this correlation, we compared analyses run with exclusion at a serum conversion of 5 mg/L to analyses run with exclusion at serum 10 mg/L and the results were similar. This indicates that the model is robust

to the choice of CRP cutoff value. All analyses presented in this paper were run using raw DBS CRP values. For ease of interpretation serum conversion values are reported in the manuscript unless otherwise noted.

Hemoglobin A1c (HbA1c) is a measure of average blood glucose values over the past 3 months. HbA1c also required a 6 mm DBS punch. Each punch was eluted in 400µL MULTIAGEN Hemoglobin Denaturant for 14 hours. The Architect blood chemistry analyzer was loaded with a cuvette with eluent and was then used to determine HbA1c and total hemoglobin by measuring absorbance at 700nm for HbA1c and 604nm for total hemoglobin. The analyzer's program calculated percent HbA1c using the following formula: $[(\text{HbA1c}/\text{TotHb})\times 100] - 3+(0.2 \times \text{TotHb})$.

There is no published description of the lab processes with the China data but they used standard protocols (Kowal, Chatterji, Naidoo, Biritwum, Newell, et al., 2012).

Variable Creation

We created groups based on a combination of HbA1c value and diabetes diagnosis status. If participants answered “yes” to “Have you ever been diagnosed with diabetes (high blood sugar)?” and had an HbA1c level that was considered at target (below 6.5) according to guidelines (American Diabetes Association Professional Practice Committee for Diabetes, 2025) then they were placed into the “At Target Diabetes” (ATD) group. If participants answered “yes” and had HbA1c level above target (at or above 6.5) according to guidelines (Ibid), they were placed into the “Not At Target Diabetes” (NATD) group. If participants answered “no” and their HbA1c was below 5.7 they were placed into the “No Diabetes” (ND) group and if they answered

"no" and their HbA1c was between 5.7 and 6.5 they were placed in the "Prediabetes" (PD) group. See Tables 1 and 2 for a summary of these groups in each country.

Tables 1 and 2 present the descriptive statistics for our sample by country. There were more females than males in our sample. The at-target diabetes (ATD) group is small in each country (n = 76 in Mexico, n = 285 in China) compared to other groups, but large enough to run the regression. While we left HbA1c continuous in our regression model, we report the size of each clinically relevant grouping of HbA1c:

At Target Diabetes (ATD) – Diagnosed with diabetes, but HbA1c < 6.5%

Not At Target Diabetes (NATD) - Diagnosed with diabetes and HbA1c > 6.5% (note that the true target for HbA1c is 7%, but to keep comparison with people who do not have diabetes as clear as possible, we have used the 6.5 cutoff)

Prediabetes (PD) – No diagnosis of diabetes and HbA1c > 5.7 % and < 6.5%

No Diabetes (ND) – No diabetes diagnosis and HbA1c < 6.5%

We ran independent sample t-tests as initial assessments of the relationship between HbA1c and CRP.

Table 1: Descriptive Statistics - China

Characteristic	**N = 6,050**
	M (CI)
CRP	0.76 (mg/L) (0.46, 1.70)

HbA1c	5.44% (4.95, 5.75)
	N(%)
Sex	
Male	2,936 (49%)
Female	3,107 (51%)
Age	61 (55, 69)
Diabetes Status	
ATD	285 (4.8%)
NATD	470 (7.9%)
ND	4,264 (72%)
PD	943 (16%)

Table 2: Descriptive Statistics - Mexico

Characteristic	**N = 1,871**
	M (CI)
CRP	1.23 (mg/L) (0.76, 2.13)

HbA1c	5.80% (5.42, 6.57)
	N(%)
Sex	
Male	733 (39%)
Female	1,137 (61%)
Age	67 (61, 75)
Diabetes Status	
At Target Diabetes	76 (4.2%)
Not At Target Diabetes	485 (27%)
No Diabetes	787 (43%)
Prediabetes	468 (26%)

Statistical Analysis

All analyses were run separately for each country because of different biomarker collection methods. We analyzed difference in CRP among every combination of the four groups (ATD, NATD, PD, ND) through independent samples t-tests. Then, we ran linear regressions with CRP and HbA1c moderated by diabetes status. We ran a second set of regressions wherein

we included control variables (age and sex). The comparison of interest was that between the ATD group and the ND group. All other comparisons are available in the appendix. We controlled for sex and age because of their well-established positive relationship with CRP (Khera et al., 2009; Siemons et al., 2014).

We used R (Version 4.2.2; R Core Team, 2022) for all our analyses[3].

We were faced with a decision point as to use diabetes diagnosis or diabetes itself. Figures 1 and 2 depict the slopes for each group. Given, that our emphasis is on physiological changes in inflammation as a result of diabetes, and there are large numbers of undiagnosed individuals in both countries, we determined that we would use diabetes status and include people without a diagnosis, but an HbA1c indicating diabetes in the "yes" diabetes group.

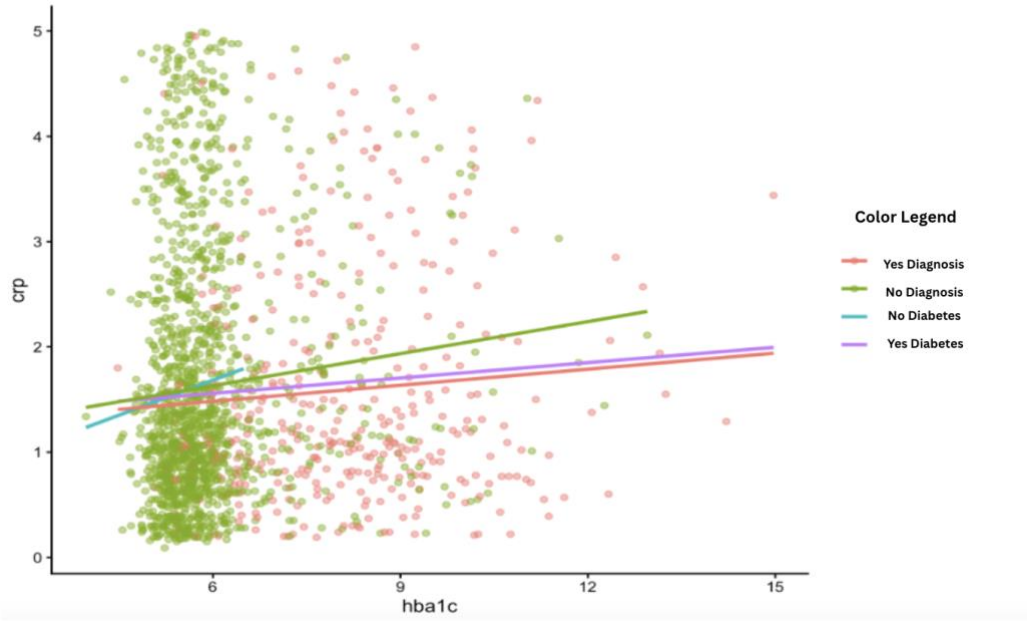


Figure 4: Scatterplot and slope of diagnosis status and diabetes status in Mexico. Lines show that people who have not been diagnosed, but have diabetes are influencing the slope of the "no group". Since our research question is not focused on access to diagnosis, but rather on the physiological effects of diabetes itself, we chose to focus on grouping that establish whether or

not someone has diabetes (either through a diagnosis or an HbA1c that indicates diabetes, even if they do not have a diagnosis).

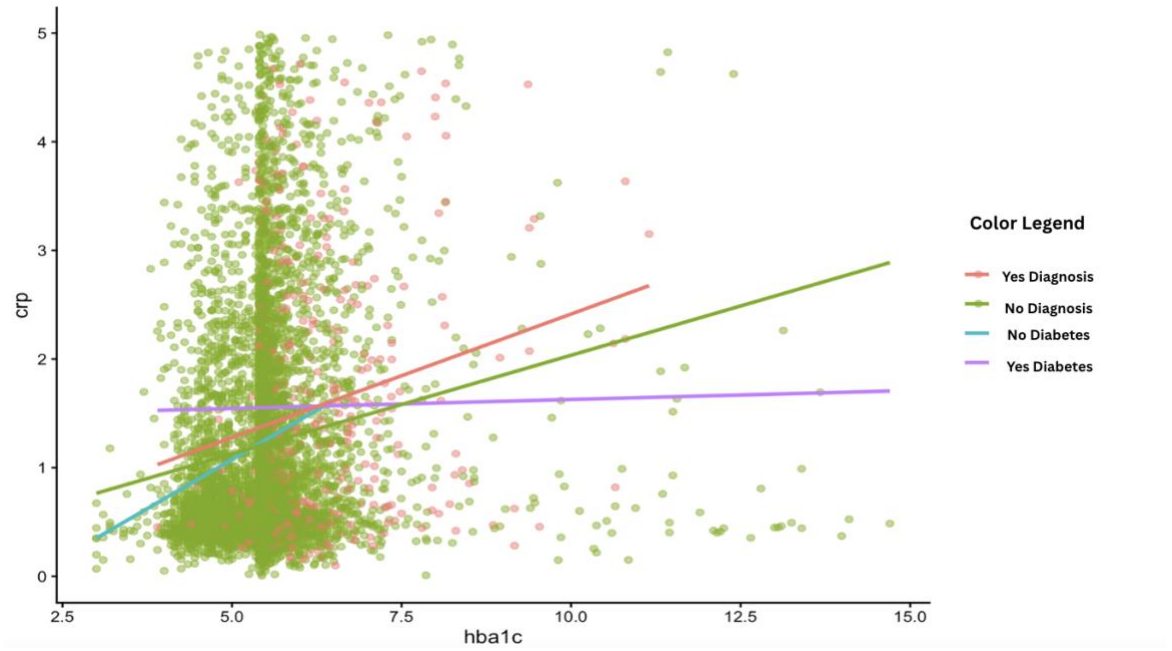


Figure 5: Though quite different from the Mexico data, when comparing the slopes of the diagnosis variable versus all diabetes (based not just on diagnosis but also HbA1c above 6.5%, we see a clear difference in which undiagnosed individuals have a strong influence on the slopes and thus create noise for our analysis that is focused on physiology and not access to care.

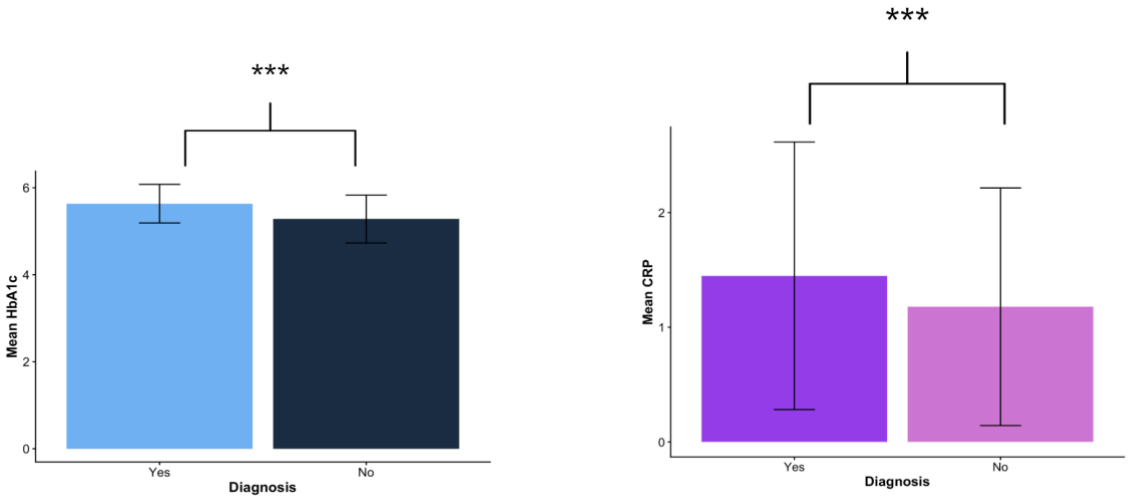
Results

Comparisons among all people with HbA1c levels below the diagnostic cutoff for diabetes

China

In China CRP was normally distributed, but HbA1c was not. HbA1c was not log transformed for a number of reasons: to log transform HbA1c removes meaningful values without a strong added benefit, the difference from one HbA1c value to the next is meaningful while orders of magnitude are not, and while it is only required for the outcome variable, the

residuals for HbA1c were within an acceptable range of normally distributed. Under the threshold of HbA1c 6.5%, people with a diabetes diagnosis had higher HbA1c on average (M = 5.6%) than people with no diabetes (M = 5.3%) $t(5{,}506) = 10.6$, $p < .05$. People with a diabetes diagnosis also had higher CRP levels (M = 1.45) than people with no diabetes (M = 1.18).

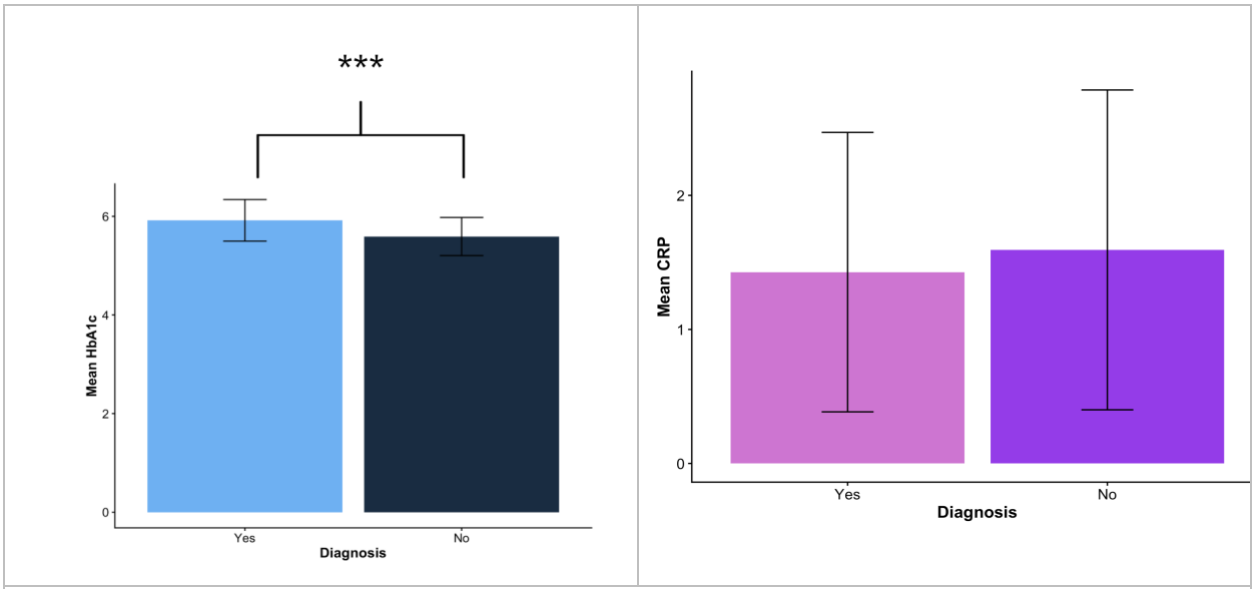


Note: * $p < .05$, ** $p < .01$, *** $p < .001$

Figure 6: Mean CRP and Mean HbA1c among diabetes status groups in China

Mexico

In Mexico CRP and HbA1c have a positive correlation $r(1{,}846) = 0.06$, $p = .012$. Both were normally distributed. Under the threshold of HbA1c 6.5%, people with a diabetes diagnosis had higher HbA1c on average (M = 5.9%) than people with no diabetes (M = 5.6%) $t(1{,}298)$ = 6.9, $p < .05$. There was no significant difference in CRP levels between people with diabetes (M = 1.40) and people with no diabetes (M = 1.59).



Note: * $p < .05$, ** $p < .01$, *** $p < .001$

Figure 7: Mean CRP and Mean HbA1c among diabetes status groups in Mexico

We ran linear regression models with and without covariates (age and sex/gender) with CRP predicted by HbA1c moderated by diabetes status. Tables 3 and 4 show the full results. In Mexico the interaction was non-significant. This non-significance aligns with the complexity of the above pictured relationships between average CRP, HbA1c, and diabetes status in Figure 4: people with diabetes and an HbA1c below 6.5 still had higher HbA1c on average but their CRP was the same. The CRP level of people with no diabetes is relatively high.

Table 3: Diabetes Status Moderating the Relationship Between CRP and HbA1c in Mexico

Characteristic	Beta	95% CI	p-value
Diabetes			
No	—	—	
Yes	0.88	-0.19, 2.0	0.11
HbA1c	0.22	0.05, 0.39	0.01
Diabetes * HbA1c			
Yes * HbA1c	-0.17	-0.35, 0.01	0.064

Abbreviation: CI = Confidence Interval

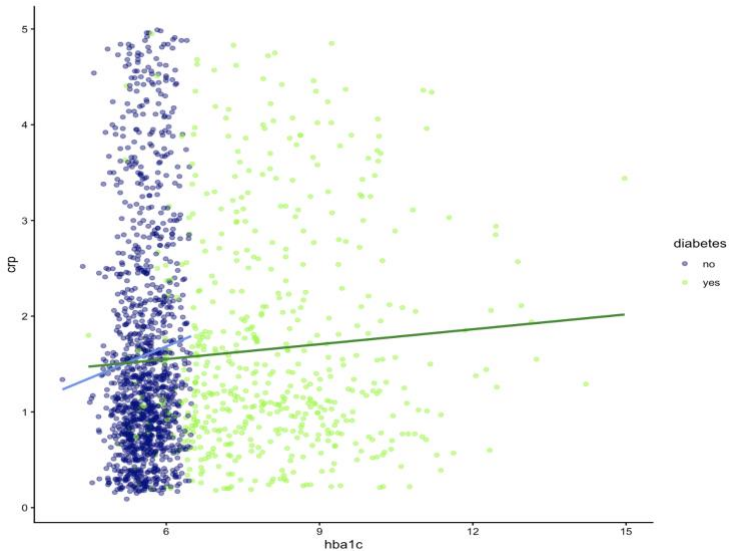


Figure 8: Slope of CRP and HbA1c by Diabetes Status in Mexico

In China, the interaction is significant and we can see it visually in the flattening of the slope in the diabetes group (Figure 9).

Table 4: Diabetes Status Moderating the Relationship Between CRP and HbA1c in China

Characteristic	Beta	95% CI	p-value
Diabetes			
No	—	—	
Yes	2.2	1.8, 2.6	<0.001
HbA1c	0.36	0.31, 0.41	<0.001
Diabetes * HbA1c			
Yes * HbA1c	-0.35	-0.42, -0.28	<0.001

Abbreviation: CI = Confidence Interval

Figure 6:

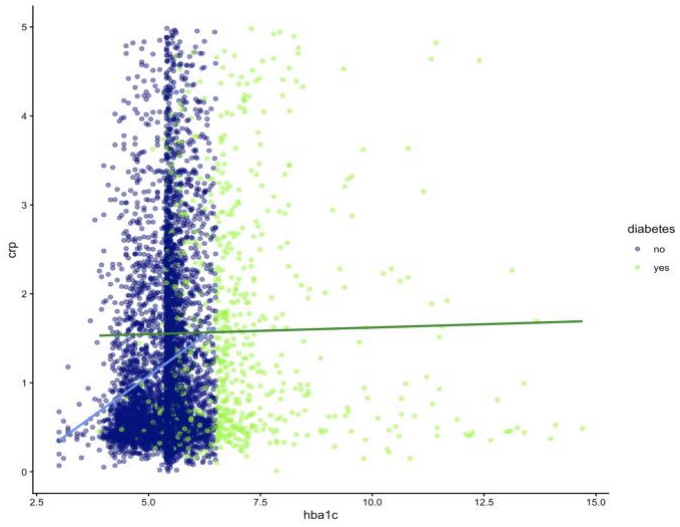


Figure 9: Slope of CRP and HbA1c by Diabetes Status in China

Table 5: Diabetes Status Moderating the Relationship Between CRP and HbA1c in Mexico Controlling for Age and Sex

Characteristic	Beta	95% CI	p-value
Diabetes			
No	—	—	
Yes	0.77	-0.29, 1.8	0.2
HbA1c	0.2	0.03, 0.37	0.022
Sex			
Male	—	—	
Female	0.24	0.13, 0.35	<0.001
Age	0	-0.01, 0.00	0.11
Diabetes * HbA1c			
Yes * HbA1c	-0.15	-0.33, 0.03	0.1

Abbreviation: CI = Confidence Interval

Table 6: Diabetes Status Moderating the Relationship Between CRP and HbA1c in China Controlling for Age and Sex

Characteristic	Beta	95% CI	p-value
Diabetes			
No	—	—	
Yes	2.1	1.7, 2.5	<0.001
HbA1c	0.36	0.31, 0.41	<0.001
Sex			
Male	—	—	
Female	0.08	0.03, 0.13	0.004
Age	0.01	0.01, 0.01	<0.001
Diabetes * HbA1c			
Yes * HbA1c	-0.34	-0.41, -0.27	<0.001

Abbreviation: CI = Confidence Interval

Discussion

Interpretation of Findings

Overall, we found mixed support for a relationship between inflammation and HbA1c. We first hypothesized that PWD at target HbA1c (< 6.5%) would have higher CRP on average than people who do not have diabetes. We were able to reject the null hypothesis in China, but not in Mexico. In China, among all people with an HbA1c below 6.5, the people who had a diabetes diagnosis had significantly higher HbA1c. In Mexico however, people with prediabetes had higher HbA1c than people with diabetes. When we removed people with prediabetes, we

observed significantly higher mean CRP among people with diabetes compared to people who do not have diabetes.

Similarly, with our second hypothesis, that there is a significant difference in the relationship between CRP levels and HbA1c among all people with no diabetes versus all people with diabetes, this was supported in China and not in Mexico. Given our hypothesis that people who have ATD are still experiencing physiological dysregulation that could be captured by inflammation, if the null hypothesis is rejected, we would expect the slope of the line expressing the relationship between HbA1c and CRP to be flatter among the group with diabetes. The flattening of the slope is very clear in the China data, and less clear in the Mexico data, but still trending flatter (see Figures 8 and 9). Mexico had more complexity, that obscured the clarity of this pattern, but it did not deviate completely. Therefore, our third hypothesis was not supported, because the countries do not align. However, it is likely that we would see more alignment if we were able to include additional sources of variability in inflammation beyond HbA1c and diabetes status.

Implication of These Findings

In people without diabetes it has been found that every increase in HbA1c is associated with an increased risk in CVD (Butalia et al., 2024), so the fact that the people with diabetes under 6.5% still had a significantly higher HbA1c than those who do not is clinically meaningful. Large bodies of research have linked inflammation with cardiovascular disease (CVD; Henein, Vancheri, Longo, & Vancheri, 2022), diabetes (Rohm, Meier, Olefsky, & Donath, 2022), autoimmune diseases (Bellocchi et al., 2022), and pulmonary diseases (e.g., asthma and lung disease) (Marya & Patel, 2021). Inflammation measured specifically through C-reactive protein (CRP) has linked it to renal failure (Choi & Yang, 2024), post-menopausal breast cancer (Jiang

et al., 2024), neuropsychiatric diseases (Bao et al., 2024), ovarian cancer (Zeng et al., 2016), overall survival in hepatocellular carcinoma (Zheng et al., 2013), and death in chronic dialysis patients (Iseki, Tozawa, Yoshi, & Fukiyama, 1999). Nearly two thirds of people with T2D are expected to die from CVD ("ESC Guidelines", 2014), and one component of this connection may be CRP (Esser, Paquot, & Scheen, 2015). Despite the strength of these connections between disease and inflammation, there may be mechanisms at play in the pathophysiology of diabetes that go beyond them that prove inflammation to be an insidious precursor and ever-present antagonist in the span of diabetes progression.

Limitations

A critical component of the findings in the ACCORD trial and the United Kingdom Prospective Diabetes Study (UKPDS) is that the effects of intense diabetes therapy took time to emerge in many cases. One of the greatest weaknesses of our study is that we do not have information on the duration of diabetes. Time spent with the disease and time spent on various medications are likely critical in explaining the patterns that have been recorded here. One other notable limitation is that the sex variable was determined through the researcher's visual assessment and participants were not directly asked about this variable.

Conclusion

These findings contribute to a growing body of evidence that inflammation is tied to the pathophysiology of diabetes and may hold value as both a treatment target and is a biomarker that should be monitored in all people with diabetes in order to better understand the intricacies of the relationship between the two, and ultimately to enable better tracking of disease progression and prevention of death and co-morbidities. Beyond the antecedent increase in inflammation known to manifest in the presence of diabetes, it has been proposed that

inflammation may be a driving force that initially pushes the body out of a euglycemic state and is a pivotal component of diabetes etiology prior to the disease state. It is difficult to test this without immense longitudinal data, but regardless of the timing of when inflammation becomes a critical characteristic of diabetes, it is an imperative mechanism that warrants better understanding than we have currently. More research needs to dig deeper into this connection both through analysis of existing datasets like we have done here, but also through a renewed commitment to monitoring and documenting inflammation levels in people known to have and at high risk for diabetes.

Bridge to chapter III

In this chapter II have examined the connections between HbA1c and inflammation in two populations that have clear, important differences that this analysis cannot explain. In the following chapter, I will apply a more advanced statistical model to the same data in an attempt to better characterize the observed connection between diabetes and inflammation. In this next chapter, I will examine inflammation in the context of all chronic diseases that were measured in SAGE rather than focus explicitly on diabetes. This is a critical additional step since the contribution of other chronic diseases to overall inflammation certainly interferes with the relationship between inflammation (CRP) and HbA1c.

CHAPTER III: DEMONSTRATING MULTICATEGORICAL MAIHDA'S POTENTIAL FOR STUDYING MULTIMORBIDITY AND CHRONIC INFLAMMATION: A PROOF OF CONCEPT USING DATA FROM THE STUDY ON GLOBAL AGEING AND ADULT HEALTH (SAGE)

Tian Walker, Aarón Salinas Rodríguez, Betty Soledad Manrique Espinoza, Ricardo Robledo, Salvador Villalpando, Fan Wu, Yanfei Guo, Yong Jiang, Min Yu, Xinjian Li, Yang Zheng, Jiying Xu, Alicia M. DeLouize, Nirmala Naidoo, Paul Kowal, J. Josh Snodgrass, and Clare R. Evans

The WHO teams who carried out data collection included Aarón Salinas Rodríguez, Betty Soledad Manrique Espinoza, Ricardo Robledo, Salvador Villalpando, Fan Wu, Yanfei Guo, Yong Jiang, Min Yu, Xinjian Li, Yang Zheng, and Jiying Xu. The WHO administrative team included Nirmala Naidoo, Paul Kowal, Alicia M. DeLouize, and J. Josh Snodgrass. I was the primary contributor to the research design and writing. Clare Evans was consulted heavily on the statistical design and the visualization. She also provided multiple rounds of edits. J. Josh Snodgrass provided edits and intellectual support during the writing process.

Abstract

Background: The slow-motion epidemic of non-communicable diseases (NCDs) continues to take its toll on population health globally and is particularly harmful to older adults. Most often NCDs do not occur in isolation and yet we lack a systematic way to analyze comorbidity along with health outcomes of interest.

Methods: Using data from China and Mexico in the World Health Organization's Study on global AGEing and adult health (SAGE), we utilize a novel approach to a multilevel modelling—multicategorical Multilevel Analysis of Individual Heterogeneity and Discriminatory Accuracy (M-MAIHDA)—to evaluate patterns of inflammation levels among all

unique combinations of gender and disease status for diabetes, hypertension, pulmonary issues, and arthritis.

Results: Chronic low-grade inflammation levels (measured by CRP) were significantly higher among women in Mexico (by 0.26 mg/l, 95%CI [0.15, 0.37], and among women (by 0.12 mg/l, 95%CI [0.04, 0.20]) and people with diabetes (by 0.38 mg/l, 95%CI [0.28, 0.47]) and hypertension (by 0.21 mg/l, 95%CI [0.13, 0.29]) in China. Broadly, the MAIHDA models revealed that the presence of diabetes and another comorbidity correlates with higher CRP than any other disease combinations or individual NCDs.

Conclusion: This application of MAIHDA allows for a multidimensional assessment of the complex relationships among comorbid NCDs and inflammation. Results indicate that people with diabetes and any additional NCD may represent a particularly high-risk group. This statistical approach can be applied in similar ways to expand our capacity to examine multimorbidity and health outcomes.

Introduction

The slow motion epidemic of non-communicable diseases (NCDs) continues to take its toll on population health globally (Afshar et al., 2015; Arokiasamy et al., 2015; United Nations, 2025). The combination of an aging global population (Jarzebski et al., 2021; Leckie et al., 2025) and high rates of NCDs among them (Marengoni et al., 2011) has been a key driver of this trend. In addition to the substantial human costs of NCDs in terms of morbidity and early mortality (Shu & Jin, 2023), the financial and economic burdens of NCDs to individuals (Jaspers et al., 2015) and economies (Muka et al., 2015) make addressing NCDs a critical goal for health and economic policy.

One critical and under-explored aspect of NCDs is their co-occurrence, particularly with diseases known to co-occur such as diabetes and heart disease. Despite the fact that more than 80% of people who have NCDs have more than one (Boyd et al., 2012), few statistical methods systematically assess and monitor the potential multiplicative harms of multimorbidity (Charlson & Wells, 2022). This is especially true in older populations, which tend to experience multimorbidity at higher rates (Bektas et al., 2018; Kowal et al., 2015). Instead, most published research has focused on one disease at a time (Boyd et al., 2012; Skou et al., 2022), or excluded people with comorbidities because of methodological restrictions related to generalizability (Gross et al., 2002; He et al., 2020; Van Spall et al., 2007). Researchers who are interested in investigating co-occurring conditions have been hampered by limitations with conventional statistical approaches and small sample sizes, leaving the documentation and pathophysiological understanding of comorbidity under-examined (Charlson & Wells, 2022; He et al., 2020).

A recently developed approach, Multilevel Analysis of Individual Heterogeneity and Discriminatory Accuracy (MAIHDA) (C. R. Evans, 2015; C. R. Evans et al., 2018; C. R. Evans,

Leckie, et al., 2024) has shown tremendous promise for overcoming these limitations and enabling future exploration of co-occurring conditions. However, to date, MAIHDA has primarily been used to explore inequalities between populations (intersectional MAIHDA, or I-MAIHDA). I-MAIHDA leverages the advantages of multilevel models in a new formulation, nesting individuals (level 1) within analytic strata (level 2) defined by intersectional combinations of identities and positionalities (e.g., gender, race/ethnicity, education), in order to obtain robust predictions for strata even when sample sizes are small (C. R. Evans, Borrell, et al., 2024).

Previous publications have called for applications of MAIHDA to examine "combination complexity" for comorbid conditions (Merlo, 2018). While there is tremendous excitement for this idea, empirical demonstrations have been rare (Rodriguez-Lopez et al., 2023). We answer that call and advance an extension of MAIHDA for considering high-dimensional interactions and complex combinations of conditions (multicategorical MAIHDA, or M-MAIHDA).

The analyses in the present article demonstrate how multicategorical MAIHDA can be used to address high-dimensional interactions of entangled health issues, and apply the approach to assessing chronic inflammation across combinations of comorbid NCDs for men and women. Our analyses were repeated and compared across samples recruited from aging populations in China and Mexico who participated in wave 1 of the WHO's Study on Global AGEing and Adult Health (SAGE). As part of the demonstration, we discuss the advantages MAIHDA offers over other methods for this type of research question and examine the relationships that would likely go undetected with more traditional approaches.

Inflammation and Non-Communicable Disease Multimorbidity

Chronic systemic inflammation has consistently been linked with multimorbidity as well as with common comorbid NCDs (Bektas et al., 2018). However, inflammation has a complex and not particularly well understood causal relationship with NCDs. For instance, the consistent and strong positive correlation between inflammation and NCDs could exist because NCDs increase inflammation, or because inflammation contributes to the etiology of NCDs (Camps & García-Heredia, 2014). It is also possible that some underlying causes (perhaps related to environmental exposures, diet, or infection) could contribute to both NCD development and inflammation (McDade, 2012), and to the extent that inflammation shows up earlier, it may serve as a "canary in the coal mine", indicating progression toward NCD development but not a direct cause or mediator (Bektas et al., 2018). These mechanisms also may not be mutually exclusive, and inflammation and NCDs could be mutual drivers through positive feedback loops.

Research on the relationship between inflammation and NCDs is further complicated by the fact that the relationship(s) might differ across NCDs—for instance, while inflammation has known correlation with diabetes (Rohm et al., 2022), cardiovascular disease (CVD) (Henein et al., 2022), pulmonary-related disease (Marya & Patel, 2021), and arthritis (Spel & Martinon, 2020), the magnitude of this correlation likely differs for different NCDs. Layered on this is the compounded complexity of co-morbidity—do the processes stack on each other in an additive way, or are their interactions multiplicative (e.g., inflammation related to diabetes + inflammation related to asthma + inflammation related to having *both*)? There is strong evidence in the literature that the effects of multiple NCDs are compounding and the presence of multiple NCDs has even been named a proxy for accelerated ageing (Bektas et al., 2018).

The goal of the present analysis is to demonstrate an approach for studying multi-dimensional, complex, physiological processes tied to disease development and progression with

a special interest in what this might reveal about diabetes, multimorbidity, and chronic inflammation. Specifically, this analysis investigates how inflammation levels differ across subgroups defined by combinations of four NCDs (diabetes, hypertension, pulmonary issues, and arthritis) and gender. Using data from two countries (Mexico and China) included in SAGE, we fit a series of multicategorical MAIHDA models to examine patterns of C-reactive protein (CRP) across analytic strata subgroups. CRP is a minimally-invasive, relatively low-cost biomarker for chronic low-grade inflammation (Brindle et al., 2010; McDade et al., 2004). CRP has been used extensively in research on inflammation and NCDs and has been established as a reliable indicator of increased disease risk (Banait et al., 2022; Sáenz-Ravello et al., 2024; Wiebe & Tonelli, 2025). The working hypothesis was framed as an expectation for higher CRP levels among subgroups with multiple chronic diseases and lower CRP levels among those with few or no chronic diseases. This study is therefore exploratory and descriptive.

Methods

Sample

Data for this analysis comes from Wave 1 of SAGE (Kowal et al., 2012). SAGE was designed to better understand disease burden among ageing and older persons in middle income countries. Another goal of SAGE was to expand knowledge about multimorbidity beyond high-income countries (Kaluvu et al., 2022). Data from SAGE wave 1 (2008-2010) from China and Mexico was used for the present analysis (Biritwum et al., 2013; Kowal et al., 2012), as the data from these countries contain two biomarkers of interest, CRP and glycated hemoglobin (HbA1c). In both samples, we included persons who answered self-report questions about disease symptoms and diagnosis and underwent biomarker collection with dried blood spots to measure CRP and HbA1c. In China, the publicly available dataset included a full sample of 15,550, with

n=6,832 having at least one CRP measurement available. For details on exclusions see Appendix A. Respondents were excluded if we were unable to determine their status for any one of the four NCDs included in the study: diabetes, hypertension, breathing issues, or arthritis. The final sample sizes were n=5,883 in China and n=1,778 in Mexico.

While China and Mexico have some similarities, such as high disease prevalence and complex environmental and social determinants that shape these outcomes, their differences are useful to our present analysis. By including two very different countries and comparing results across them, we avoid making any implicit assumptions that patterns we observe in chronic inflammation across disease status categories are universal and generalizable. SAGE had country-specific review approvals as well as approval from the WHO Ethical Review Committee (Kowal, Chatterji, Naidoo, Biritwum, Newell, et al., 2012).

Dependent Variable: CRP

CRP was evaluated using dried blood spot (DBS) collection. For details on procedures, see Appendix B. Importantly, CRP measured with DBS may not be comparable with CRP measured in other studies using venipuncture. Possible CRP values in this study range from 0-5 mg/L.

Independent Variables

Details of survey procedures and non-blood biomarker collection are described elsewhere (Dona et al., 2020; Kowal, Chatterji, Naidoo, Biritwum, Newell, et al., 2012). A complete case analysis was conducted. Participants with missing values on gender or any of the diseases were excluded from the analysis.

Gender

Interviewers indicated participant gender status dichotomously based on appearance during the interview. Therefore, this variable is the closest proxy for gender (social determinants) and sex, itself a proxy for hormonal differences, considered critical when studying health and disease (Juster et al., 2025).

Diabetes

Hemoglobin A1c (HbA1c) is a measure of average blood glucose level over the past 3 months, based on the amount of glucose attached to red blood cells known as glycated hemoglobin (M. Wang & Hng, 2021). We created dichotomous groups based on a combination of HbA1c value and self-report of past diabetes diagnosis. If participants answered "Yes" to "Have you ever been diagnosed with diabetes (high blood sugar)?" or their HbA1c was ≥6.5%, then they were coded as "Yes" (diabetes=1). Otherwise, they were coded as "No" (diabetes=0).

Hypertension

We created a dichotomous variable for hypertension (Yes=1, No=0) based on previous diagnosis with hypertension or mean blood pressure ≥140/90 mmHg (averaged over 3 separate readings).

Pulmonary Issues

We constructed a dichotomous "pulmonary issues" variable by combining two variables, self-reported asthma and self-reported diagnosis of lung disease (Kowal et al., 2012). Asthma was determined based on diagnosis status and a set of validated symptom-based questions (Darkwah et al., 2022) (see Appendix B for details). For chronic lung disease we only used diagnosis. If a person was Yes=1 for asthma or had a diagnosis of lung disease (Yes=1), then they were coded as Yes=1 for pulmonary issues. Otherwise, they were coded as No=0 for pulmonary issues.

Arthritis

We created a dichotomous variable for arthritis based on self-reported diagnosis (Yes=1, No=0). Previous analysis of this data found that self-reported symptoms of arthritis did not increase the cases, so we did not factor in the symptoms data (Wu et al., 2015).

Analytic Strata

By combining the five independent variables—gender and the four NCDs (diabetes, hypertension, pulmonary issues, arthritis)—each with two analytic categories, we define 32 unique analytic strata or "groups" of participants. For reference simplicity, each stratum was assigned a 5-digit ID number, with each digit corresponding to one of the five categorical variables as follows:

$$Stratum\ ID = \underset{gender}{digit\ 1} + \underset{diabetes}{digit\ 2} + \underset{hypertension}{digit\ 3} + \underset{pulmonary\ issues}{digit\ 4} + \underset{arthritis}{digit\ 5}$$

The numeric value in the digit matches the coding used above (1= Man/2=Woman for gender and Yes=1/No=0 for the NCDs). For example, stratum 21001 represents women with diabetes and arthritis, but no hypertension or pulmonary issues.

Analysis

MAIHDA models are two-level multilevel random intercepts models where individuals (level 1) are clustered within strata (level 2). In I-MAIHDA, the sociodemographic variables used to define strata (e.g., gender, ethnicity, income) are meant to capture the positionality of individuals within intersectional, interlocking systems of oppression (e.g., sexism, racism,

socioeconomic inequality). In the present multicategorical MAIHDA analysis, we structure our model similarly but define strata using gender and the four NCDs.

Following the process and supplemental R code provided in the MAIHDA tutorial (Evans et al. 2024) we started with the simplest MAIHDA model, the null or "empty" model:

Model 1: $y_{ij} = \beta_0 + \mu_{0j} + e_{0ij}$

where $[\mu_{0j}] \sim \mathrm{N}(0, \sigma^2_{\mu 0})$ and $[e_{0ij}] \sim N(0, \sigma^2_{e0})$.

The value of CRP for individual *i* in stratum *j* is represented by y_{ij}. β_0 is the intercept and represents a precision-weighted grand mean for the outcome across all strata. μ_{0j} represents the stratum-level residual (how different stratum *j*'s mean is from the grand mean), and takes a unique value for each stratum. These stratum-specific residuals collectively describe the distribution of model-predicted stratum means around the grand mean, and they are normally distributed with mean 0 (centering them on the grand mean) and variance $\sigma^2_{\mu 0}$ (the level 2 between-stratum variance). e_{0ij} is the individual-level residual, or difference between the observed value for individual *i* in stratum *j* and the stratum-specific mean. These e_{0ij} are normally distributed with mean 0 and variance σ^2_{e0} (the level 1 within-stratum variance).

The Variance Partition Coefficient (VPC) statistic is the percent of total variance at the stratum level, calculated as: $VPC = \left[\sigma^2_{\mu 0} / \left(\sigma^2_{\mu 0} + \sigma^2_{e0}\right)\right] \times 100\%$. In Model 1, the between-stratum variance ($\sigma^2_{\mu 0}$) and VPC provide two measures that help characterize the total degree of inequality or difference across strata.

Model 2 builds on this by including additive fixed effects for the categorical variables used to define the strata, as follows:

Model 2: $y_{ij} = \beta_0 + \beta_1(gender_j) + \beta_2(diabetes_j) + \beta_3(pulmonary\ issues_j) + \beta_4(hypertension_j) + \beta_5(arthritis_j) + \mu_{0j} + e_{0ij}$

where $[\mu_{0j}] \sim \mathrm{N}\ (0, \sigma^2_{\mu 0}\ )$ and $[e_{0ij}] \sim \mathrm{N}\ (0, \sigma^2_{e0}\ )$.

In Model 2, the stratum residuals μ_{0j} now account for any remaining difference between the final predicted means for stratum *j* and what would have been expected based on the additive fixed terms. Thus, the residual is analogous to an interaction term, calculated uniquely for each stratum. The main purpose of Model 2 in this study is to generate a final prediction (combining fixed beta terms and μ_{0j}) for each stratum. While either model could be used for this purpose, as they theoretically produce similar results, simulation studies suggest that Model 2 provides improvements in accuracy over Model 1 because the residual shrinkage draws estimates toward a more accurate 'starting prediction' based on the fixed values (Leckie et al., 2025).

Whereas conventional approaches to predicting outcomes might involve fitting a single-level regression model saturated with additive and interaction fixed effects sufficient to calculate a unique mean in each group, MAIHDA models benefit from the advantages of multilevel approaches. As described elsewhere (C. R. Evans et al., 2018; C. R. Evans, Leckie, et al., 2024), MAIHDA allows a flexible and scalable framework for adding strata-defining variables and categories while maintaining model parsimony. Moreover, MAIHDA predictions leverage shrinkage of residuals and precision weighting to provide more robust estimates for strata, even

when sample sizes are small. As such, MAIHDA is the preferred approach for high-dimensional interaction analyses such as this, particularly when the number of strata is large and/or the sample size (overall or in some groups) is small (Bell et al., 2019; Mahendran et al., 2022a, 2022b; Van Dusen et al., 2024).

Analyses were conducted in R version 4.4.0 (2024-04-24). The Tidyverse (Wickham et al., 2019) and lme4 (Bates et al., 2015) packages were used extensively. Linear mixed models were estimated using REML and nloptwrap optimizer.

Results

Though we are unable to directly compare CRP between the two countries due to difference in collection methods, the mean CRP tends to be higher among women and disease status groups *within* both China and Mexico (Table 7). In Mexico, these differences tend to be quite small or non-existent (for hypertension) in the raw sample with CRP levels among disease status groups too similar to compare means between those with and without each NCD. Figure 10 shows a box and whisker plot of CRP level and number of NCDs from 0 to 4. The lack of a sequential increase in CRP with each additional number of NCDs indicates that number of conditions does not unequivocally relate to higher CRP levels: it is more complex than this.

There were some significant additive effects in China, such as a statistically significant and positive effect of gender (beta = 0.12 mg/l, 95%CI [0.04, 0.20], indicating that women overall had higher levels of CRP. The effect of diabetes status is statistically significant and positive for both diabetes (+0.38 mg/l, 95%CI [0.28, 0.47] and hypertension (+0.21 mg/l, 95%CI [0.13, 0.29]), indicating that people with diabetes and hypertension had higher levels of CRP. For the full regression model results see Tables 8 and 9.

Table 7: CRP Descriptives by Country

	Mexico		China	
Strata Dimensions	n (%)	CRP Mean (SD)	n (%)	CRP Mean (SD)
Gender				
Man	700 (39%)	1.45 (1.1)	2,836 (49%)	1.18 (1.0)
Woman	1,078 (61%)	1.71 (1.2)	2,997 (51%)	1.28 (1.1)
Diabetes				
No	1,231 (69%)	1.59 (1.2)	5,098 (87%)	1.18 (1.0)
Yes	547 (31%)	1.66 (1.1)	735 (13%)	1.58 (1.2)
Hypertension				
No	765 (43%)	1.61 (1.2)	2,324 (40%)	1.11 (1.0)
Yes	1,013 (57%)	1.61 (1.1)	3,509 (60%)	1.31 (1.1)
Arthritis				
No	1,551 (87%)	1.60 (1.2)	4,697 (81%)	1.20 (1.1)
Yes	227 (13%)	1.65 (1.2)	1,136 (19%)	1.34 (1.1)
Pulmonary Issues				
No	1,585 (89%)	1.60 (1.2)	5,247 (90%)	1.22 (1.1)
Yes	193 (11%)	1.70 (1.3)	586 (10%)	1.35 (1.1)

Table 8: MAIHDA model results for Mexico

	CRP		CRP	
Fixed Effects	Estimates	CI	Estimates	CI
(Intercept)	1.62 ***	1.53 – 1.72	1.18 ***	0.98 – 1.37
Gender			0.26 ***	0.15 – 0.37
Diabetes			0.05	-0.07 – 0.17
Hypertension			-0.01	-0.12 – 0.10
Pulmonary issues			0.08	-0.09 – 0.26
Arthritis			0	-0.17 – 0.16
Random Effects				
σ^2	1.36		1.36	
τ_{00}	0.02 $_{stratum}$		0.00$_{stratum}$	
VPC(%)	2%		0%	
PCV(%)			100%	
N Strata	32			
N Respondents	1778		1778	

** p<0.05 ** p<0.01 *** p<0.001*

Table 9: MAIHDA model results for China

	CRP		CRP	
Predictors	*Estimates*	*CI*	*Estimates*	*CI*
(Intercept)	1.36 ***	1.27 – 1.46	0.97 ***	0.89 – 1.06
Gender			0.12 **	0.04 – 0.20
Diabetes			0.38 ***	0.28 – 0.47
Hypertension			0.21 ***	0.13 – 0.29
Pulmonary issues			0.1	-0.00 – 0.21
Arthritis			0.09	-0.00 – 0.17
Random Effects				
σ^2	1.12	1.12		
τ_{00}	0.05 $_{stratum}$	0.00 $_{stratum}$		
VPC(%)	4.0%	0%		
PCV(%)		94.20%		
N	32 $_{stratum}$	32 $_{stratum}$		
Observations	5833	5833		
Marginal R^2 / Conditional R^2	0.000 / 0.043	0.029 / 0.032		

** p<0.05 ** p<0.01 *** p<0.001*

In the regression table for Model 2 in China (Table 9) we see significant fixed effects for gender, diabetes, and hypertension, but the dimensionality of the relationship between these conditions and CRP is only apparent when we look at the MAIHDA graph (Figures 11-14). Figures 11 shows the values of CRP among each strata, and indicates a meaningful spread of CRP levels with some patterns that are emphasized with different color combinations highlighting Diabetes and CVD. Figure 12 highlights diabetes and pulmonary issues, and Figure 13 emphasizes diabetes and arthritis. Figure 14 shows gender clusters among the ordered stratum. As evident in Figures 11-13, the model picks up on a trend in both countries of highest CRP levels among people who have diabetes and another NCD. It requires looking at different combinations of disease conditions in order for this trend to be visible (thus an observation unique to the MAIHDA model).

Results from the China data indicate that the presence of both diabetes and hypertension, diabetes and pulmonary issues, and diabetes and arthritis are the groups with the highest levels of inflammation. Just having hypertension, pulmonary issues, or arthritis does not put a group in the higher levels of inflammation, but when any condition is combined with diabetes the result is higher inflammation levels. In Mexico, accounting for gender, the relationship between co-morbid status and CRP was identical across both genders. All of the values for women were higher, but they followed the same pattern as men (see Figure 14).

MAIHDA allows us to pick up on important relationships even when there are nuanced relationships among variables and suppression effects. In Mexico, when we look at the MAIHDA graph we can see that the order of the groups follows the same trends as in China, but the effect of gender differences makes it more difficult to pick up on. In the case of pulmonary

issues and diabetes for example, the trends align with the trends that we see in China, but it is veiled by the effect of gender.

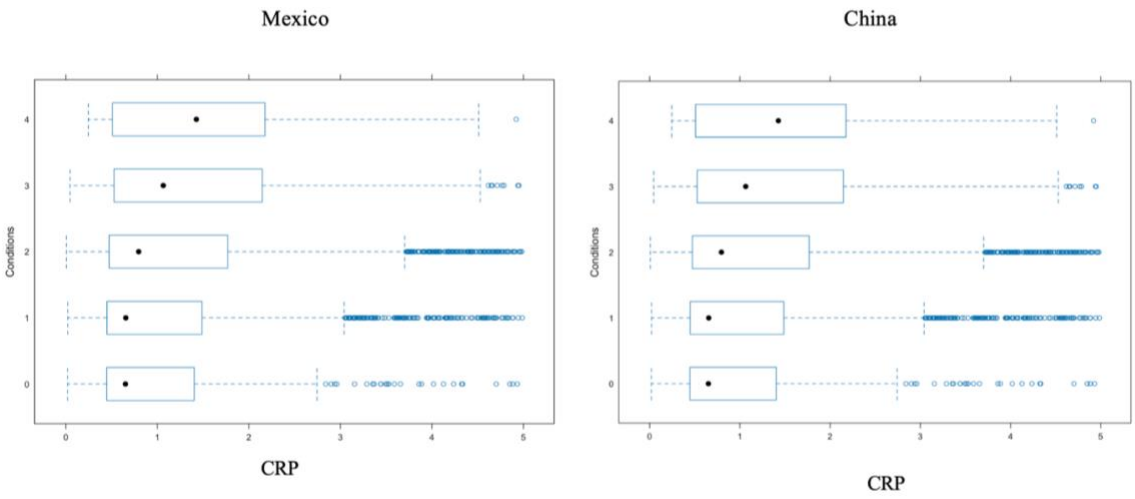


Figure 10: CRP Levels among People with 0-4 NCDs

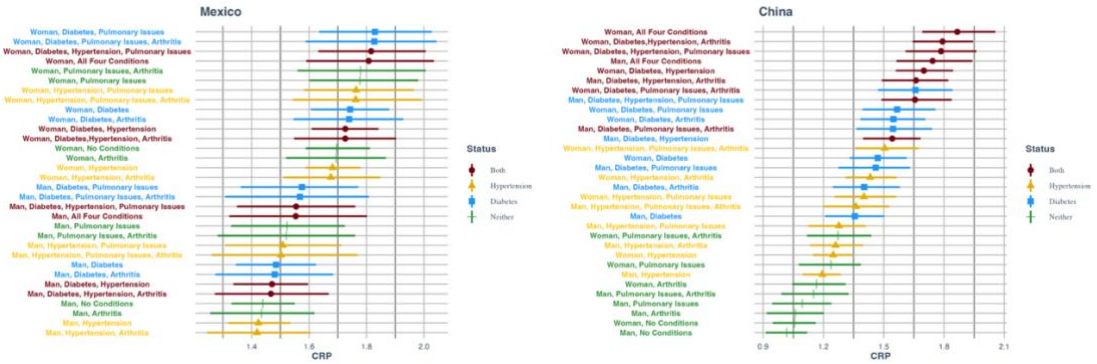


Figure 11: Stratum ordered by CRP highlighting hypertension and diabetes combinations

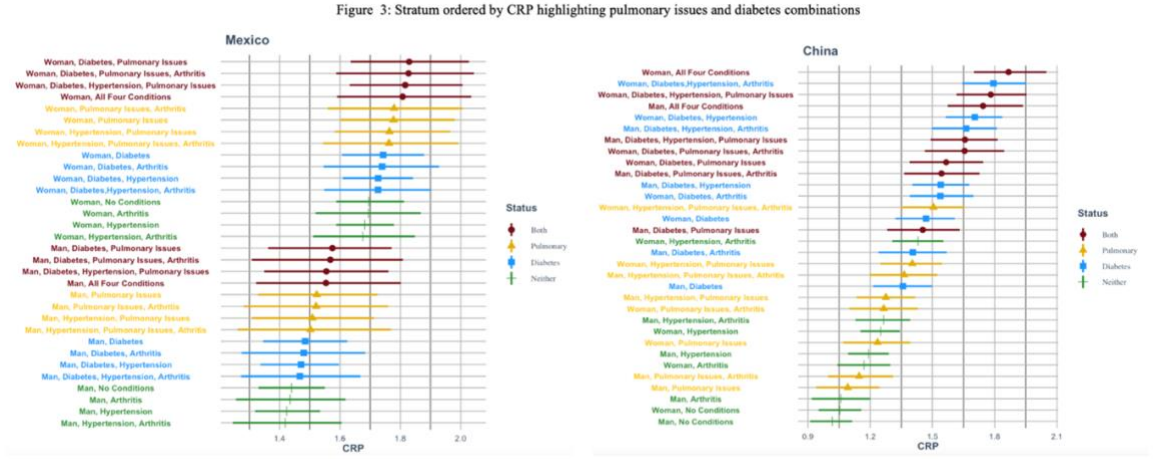


Figure 12: Stratum ordered by CRP highlighting pulmonary issues and diabetes combinations

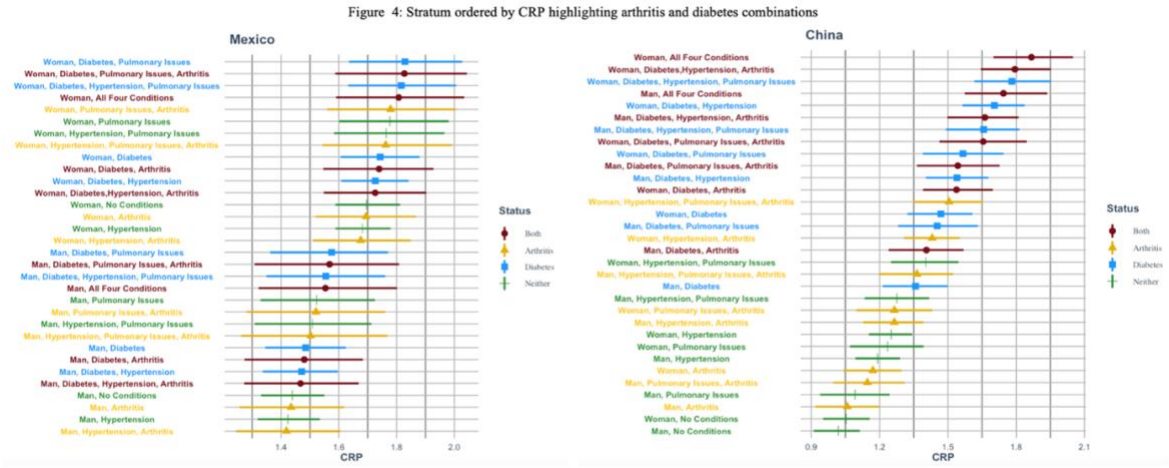


Figure 13: Stratum ordered by CRP highlighting arthritis and diabetes combinations

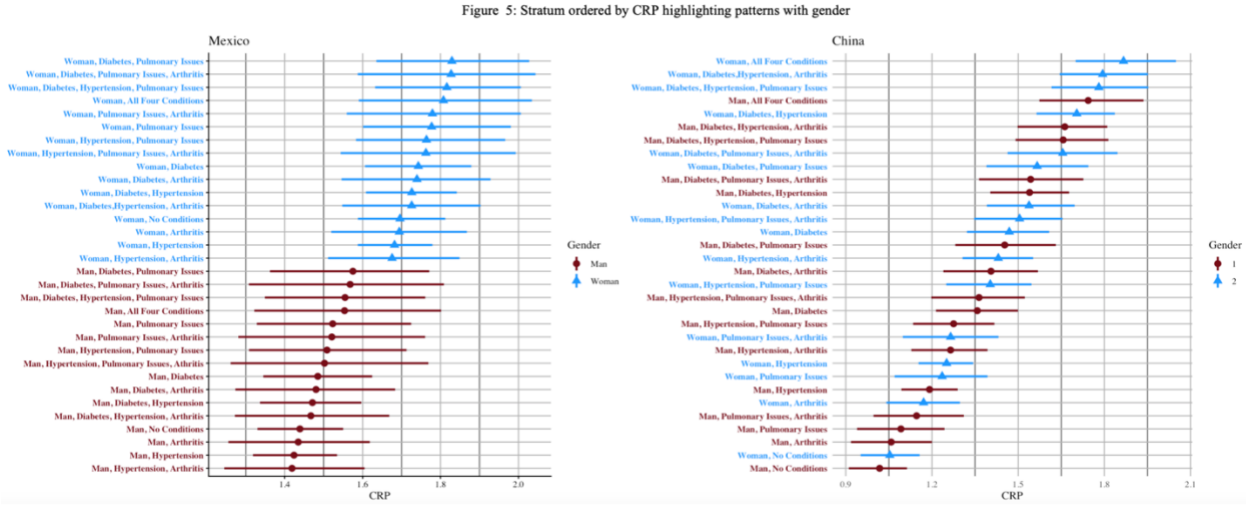


Figure 14: Stratum ordered by CRP highlighting patterns with gender

Discussion

These results indicate that there are important relationships among diabetes and the various co-morbidities, many of which would be invisible in a traditional methodological approach. The most outstanding finding here is that when treated equal to all other NCDs, diabetes stands out especially tied to inflammation. More specifically, diabetes in combination with any other NCD has the strongest correlation to inflammation. Our findings indicate that co-morbidity is particularly relevant for people who have diabetes, and preventative measures may be needed to counteract the amplified inflammatory effects of having additional conditions on top of diabetes. It is as though just diabetes, and diabetes plus other NCD indicate two levels of sickness severity, with the latter indicating a higher risk for developing more disease or dying early.

Per our expectation, inflammation and number of NCDs are not cleanly related (see Figure 10), but there are important connections between combinations of specific NCDs and inflammation. Strata that contain diabetes and an additional condition cluster in the higher CRP levels. Specifically, hypertension and diabetes among people in China and pulmonary issues and

diabetes among people in Mexico. The directionality of whether diabetes causes other conditions to result in higher CRP levels, or whether developing co-morbidities causes people with diabetes to have higher CRP is yet to be determined (Charlson & Wells, 2022).

Contextualization of Findings

Research conducted among the Indigenous Shuar in the Amazon rainforest where market integration is manifesting more slowly and lifeways and ecology are closer to those that humans evolved in, suggest that our physiological systems are designed for CRP levels to be at a baseline of 0 (McDade, 2012; Urlacher et al., 2018). Thus, while the exact meaning of a specific absolute value of CRP remains unknown, we know that all chronic inflammation is likely pathogenic, and that higher chronic inflammation is worse than lower chronic inflammation. We can interpret the results treating CRP values as continuous with the assumption that every unit increase indicates higher risks of poor health outcomes. CRP levels have been directly linked to cardiovascular disease (Pearson et al., 2003), renal failure (Choi & Yang, 2024), post-menopausal breast cancer (Jiang et al., 2024), neuropsychiatric diseases (Bao et al., 2024), ovarian cancer (Zeng et al., 2016), overall survival in hepatocellular carcinoma (Zheng et al., 2013), and death in chronic dialysis patients (Iseki et al., 1999).The addition of CRP to vascular risk score has been found to potentially improve the overall predication of vascular events (Ridker et al., 2004).

Other publications from WHO studies documented congruent findings to the gender difference that we observed in Mexico with better self-reported health by men than women in another SAGE study in South Africa (Phaswana-Mafuya et al., 2013), and higher prevalence rates of symptoms for all conditions among women in the World Heath Survey (WHS) in Burkina Faso (Miszkurka et al., 2012).

While we intentionally avoid making any implicit assumptions that patterns we observe in inflammation across disease status categories are universal and generalizable, we also would expect to see similar patterns across populations if the only factor at play was strictly physiological. Therefore, we must question what it means then that there are such stark differences between the two countries. Some likely factors are environmental pollution, health disparities, cultural norms surrounding gender roles, political upheaval and consequent tension in social relationships, and distribution of wealth and poverty.

Interpreting MAIHDA

Additionally, we extend the use of MAIHDA and demonstrate that even when all of the variance is explained by additive factors as is the case in Mexico, unlike a traditional multi-level model, this still provides us with critical insight into the relationship between diabetes and inflammation as the patterns hold true in both Mexico and China. MAIHDA allows us to capture complexity and dimensionality even when the data structure prevents us from explaining it fully. The random intercepts component of both models did not show important differences, but given the set-up of MAIIHDA this does not mean our models hold only null results. Model 2 in Mexico is the most challenging to interpret, because by traditional standards it is an overfit model. In this case however, this is meaningful and not inherently problematic. It tells us that there are no interaction effects between the different diseases and 100% of the variance is explained in the fixed effects. The China model is based on a much larger sample (~5,000 compared to ~1,000) and still only showed minimal proportional change in variance between the null model and the additive main effects model.

While we ran traditional multi-level modeling estimates for reliability including ICC and Design effect, they do not offer the usual parameter estimation used to examine multi-level

models because the clusters are categorical strata created with yes/no combinations of each disease status, and so it is impossible to take a traditional approach to surveying clustering patterns. It is important to consider MAIHDA as a novel use of multi-level modeling, that allows for an examination of interactions in the data that would be otherwise impossible. With this in mind, it is less of an issue that the ICC's for both countries were below 0.1. As expected with any null model comparison, Model 1B was found to be a statistically significant better model than Model 1A in the likelihood ratio test for model comparison ($p<.001$ in China, $p=.022$ in Mexico).

A traditional statistical approach of comparing means between groups would not have been possible in Mexico given that the mean levels of CRP are quite similar across people with and without individual diseases. However, the MAIHDA approach allows us to see patterns in the trends of the positions of strata (various combinations of NCDs and gender) relative to each other. It is through this pattern recognition that we see that groups with diabetes plus any other NCD rank among the highest levels of CRP even though the differences in CRP levels are miniscule.

Limitations

There are different environmental factors at play in each country that were not measured. Additionally, there are factors contributing to inflammation and disease that were beyond the scope of this data. Such factors include: air pollution, political turmoil, stress contributing factors specific to each culture, gender roles, dietary patterns, parasite load, and access to safe spaces to exercise. Some of these missing factors are compounding and likely explain the nuances we are picking up on, but the data available limits our ability to explore these nuances in depth.

The Mexico dataset is relatively small, and in both countries information about medication use has a lot of missingness and is complicated by the fact that among groups who are taking diabetes medication, HbA1c levels are higher and not lower. Furthermore, our data are impacted by survivor bias. As seen in Figure 10, the number of people with all 4 chronic health conditions is the smallest and this is likely due in part to people dying from one of the many health conditions that they are enduring.

There, is large variance between runs of CRP values making it impossible to ascertain meaningful comparisons to other studies based on absolute values. However, there is consensus in the literature that all increases in CRP levels are damaging and warrant increased monitoring and more awareness in the global health community. While the self-report data was nationally representative, the biomarkers are not and so the data represent populations of older adults with NCDs in each country but cannot be claimed as nationally representative. Finally, the gender variable was determined by interviewer perception and not explicitly asked and so this variable may not be completely accurate.

Conclusion

Future studies designed with MAIHDA in mind will be able to assess the relationships between NCDs and inflammation with directionality in a way that is not possible in this study both through longitudinal design and more detailed self-report of disease statuses. For example, we do not have data on the dates of when disease states began (be that through symptoms or diagnoses), and consequently we do not have data on the duration of disease nor in the case of co-morbidities, which disease occurred first. It is probable that the order of disease development would further elucidate the patterns that emerged with the use of this novel method

Future analyses using MAIHDA to study multimorbidity may be able to elucidate the currently unknown pathophysiology connecting NCDs and inflammation. MAIHDA will allow for more systemized generalizability studies designed a priori to determine whether it is necessary to consider people with multimorbidity as a separate population, and even more specifically if there are specific comorbid conditions that need to be considered when a person has them both (e.g. diabetes and hypertension).

It is incumbent on researchers to create models that can account for complex dimensionality in a robust way. The relationship between inflammation and disease is complex and therefore, it has not been thoroughly modeled statistically. Here we offer a mode through which future studies could be designed with this analysis in mind and set up robust ways to assess the multi-dimensional components of the relationship between inflammation and chronic diseases. This statistical approach can be applied in other health contexts that involve multimorbidity and syndemics as well. At the extreme of potential impact, this approach could lead to NCD prevention and treatment that targets inflammation and can also be used as a model to be applied to other public health concerns regarding simultaneously occurring diseases.

Bridge to Chapter IV

Chapter III illustrated a novel method to assess the relationship between CRP and multiple NCDs and found that even when treated like any other NCD, diabetes stood out as particularly tied to inflammation. The next chapter will change scales and move from a population level view of cellular level processes to individual experiences of people living with diabetes in the United States. The complex relationship between inflammation and diabetes offers a partial explanation of why managing diabetes is exceptionally difficult. The following

chapter assesses how PWT1D navigate the challenges of diabetes by accessing a large variety of diabetes-focused resources.

CHAPTER IV: RESOURCE ENGAGEMENT AMONG PEOPLE WITH TYPE 1 DIABETES

Tian Walker, J. Josh Snodgrass, Sara Weston

Sara Weston assisted in research design and analysis as well as provided intellectual support throughout the data collection and writing process. I am the primary contributor to data collection and writing. Sara Weston and J. Josh Snodgrass provided edits.

Introduction

Managing Type 1 diabetes (T1D) requires constant vigilance and decision making about insulin dosing, food consumption, physical activity, and mental activity. People living with Type 1 diabetes (PWT1D) typically seek information about diabetes and its management from many sources, including their clinical care team (e.g., primary care and specialist physicians), but also beyond. PWT1D may also turn to blogs, social media, books, podcasts, and peer coaches. Many of these resources are created or curated by others with T1D who are eager to share their embodied knowledge with the hope of mitigating the suffering of other people with the disease. The development and use of these resources are closely connected to patient engagement, or the degree to which people are active participants in their health care (Hibbard et al., 2004; Wolf et al., 2018). Despite widespread anecdotes of the utility of the Diabetes Online Community (DOC) and tips from other PWT1D, few rigorous scientific studies have been conducted to collectively examine which information sources PWT1D use or whether engagement with particular sources is associated with better diabetes management outcomes. In the present study, we report on a survey of PWT1D that assessed (1) what diabetes-related sources people use, (2) whether the use of specific sources is associated with better outcomes captured primarily through continuous

glucose monitors that measure blood glucose (BG) values every 5 minutes along with validated scales, and (3) whether those associations are partially explained by patient engagement.

The Medical Model of Care

Evidence-based, standard diabetes care in the US is built around an ongoing relationship with a medical provider, usually an endocrinologist who specialize in hormone-related conditions. The American Diabetes Association mandates quarterly to annual appointments for insulin-prescription renewals and glycemic monitoring (American Diabetes Association Professional Practice Committee, 2024a). However, this medical model provides limited support for day-to-day management of diabetes when unpredictable events (e.g., extreme weather or stressful social interactions) occur. Regular check-in appointments typically focus on pharmacology and clinical targets, including insulin dosing, preventing and treating complications, catering to sensitive populations, managing other medications and weight management (American Diabetes Association Professional Practice Committee, 2024b). However, in these appointments there often remains little time for the non-clinical challenges of T1D, including safe exercising, stress, and mental health, leaving an information gap for patients to navigate daily glucose rhythms largely on their own (Litchman, Rothwell, et al., 2018). It is also important to note that these challenges in the medical model of care do no not account for the challenges posed by social determinants of health including but not limited to disparities by insurance status, socio-economic status (SES), mobility, and geography. Given that this study required participants to upload data from an expensive medical device, the vast majority of participants in this study had access to care.

Peer-Created Resources

Given these gaps (and in cases outside of the scope of this study also barriers), many PWT1D are not able to reach glycemic goals (Walsh et al., 2023). Faced with a lack of information, they often turn to peer-created sources: information developed by and for people living with diabetes (e.g, Tanenbaum et al., 2021). These include blogs, social media communities, books written by PWT1D, podcasts, and structured coaching programs**.** The use of the internet as a source of information is expanding even more in present day with the advent of AI, but at the time of the study ChatGPT had only recently been released and this was less relevant.

Online Communities and Social Media

PWT1D have created vibrant online communities across multiple platforms, including Facebook groups, Reddit forums, Instagram, and Twitter/X. These spaces serve diverse functions: sharing health information and news, providing social support, coordinating advocacy efforts, and facilitating commercial engagement with diabetes products and services (Begueriesse-Díaz et al., 2017). Research suggests the online diabetes communities offer substantial benefits with minimal risk of harm, especially compared to online communities for other health conditions such as cancer and anorexia (Gloor et al., 2016; Greene et al., 2011; Hilliard et al., 2015; Kjærulff et al., 2024; Litchman, Edelman, et al., 2018).

In particular, Twitter/X has emerged as an active space where users share health information, build collective identity around the "diabetes persona," advocate for systemic change including insulin access (Bennett, 2021), and offer mutual encouragement and positivity

(Bedford-Petersen & Weston, 2021; Gabarron et al., 2019)[1]. Beyond these general-purpose social platforms, PWT1D also engage with structured resources including dedicated blogs, podcasts, books, and peer-led coaching programs.

Blogs, Podcasts, Books

T1D-focused structured content like blogs, podcasts and books written for consumption by PWT1D offer a more rigorous medium for communicating disease management information. A number of content creators have both a podcast and a blog to promote it. For example, T1D mom, Stacey Simms has all three. Another example, *The Juicebox Podcast*, has a blog as well as a private Facebook group where users can connect. There are also books like *Think Like a Pancreas*, which is written by a PWT1D who is also a certified diabetes care and education specialist (CDCES). These types of resources have been expanding in recent years. Dozens of popular press books (not counting diet and recipe books) have been written in the last 10 years by people living in close proximity to the disease (be that living with it themselves, raising a child who has it, or working as a medical care provider) with the intention of making life with T1D safer and more manageable. Podcasts, books, and blogs written by non-medical PWT1D refrain from offering medical advice and instead provide examples of how one might medically treat diabetes through personal testimonies of successful approaches to disease management.

[1] However, we note that Twitter may have an outsized research literature due in part to the ease with which researchers could scrape information; other social media outlets have restricted such data access, limiting options for study. Moreover, Twitter/X has since changed its API policies, and subsequently has received less attention by academic researchers.

This approach avoids liability constraints while offering rich information on disease management. Much of the advice and experiences on these podcasts is not sanctioned by the FDA, such as micro-dosing (injecting small amounts of insulin in anticipation of high blood sugar) also known as being "bold with insulin" (Benner, 2015).

Non-Profit Organizations

Non-profit organizations committed to bettering the lives of people with T1D like Juvenile Diabetes Research Foundation (JDRF), now Breakthrough T1D, and Beyond Type 1 are one main way that PWT1D find each other. Smaller non-profits like Type One Run, Beta Cell Foundation, Children with Diabetes, College Diabetes Network, You're Just my Type, and local non-profits like Pediatrics-Adolescent Diabetes Research Education (PADRE), Mama I'm Low, and Diabetes Community Care Team (to name a few) are also working to grow T1D community. These groups serve as outlets for sharing diabetes information and are one of the main ways that people with T1D can find out about ongoing research they may want to participate in.

Patient Engagement as a Mechanism for Improved Outcomes

The proliferation of these peer-created resources may both reflect and reinforce patient engagement, or the degree to which people willingly manage their own health and care (Hibbard et al., 2004; Wolf et al., 2018). Patient engagement – sometimes referred to as patient activation – involves: the valuation of one's own health; knowledge about one's bodily and medical needs; adherence to medical instructions; and confidence in seeking and advocating for oneself (Wolf et al., 2018).

To date, there is little work assessing the relationship between patient engagement and health outcomes in the PWT1D population. One systematic review of patient engagement found

evidence for improve glycemic control, but this study did not distinguish between Type 1 and Type 2 diabetes (Simmons et al., 2014). Evidence from a study of adolescents with Type 1 suggest that perceptions of control and confidence (aspects of patient engagement) are associated with adherence and metabolic control (Croom et al. 2011). These studies suggest that patient engagement is beneficial to medical outcomes for PWT1D.

There is also reason to suspect that some sources of diabetes-related information may improve patient engagement through empowering PWT1D. In other words, receiving more information about T1D and hearing first-hand accounts from those who have successfully managed their conditions may foster feelings of confidence around one's ability to manage diabetes. While little is known specifically about the use and effects of the various peer-created resources described above, in the present paper we hypothesize that some resources will be associated with greater feelings of patient engagement, which in turn will lead to better management and clinical/psychological outcomes for PWT1D.

Current Study

Despite the proliferation of peer-created diabetes resources, rigorous research examining their use and impact is limited. It is unknown whether these resources constitute a meaningful source of information for people with T1D, to what extent people with T1D use them in comparison to more traditional medical resources, and whether the use of these resources has a measurable impact on health and well-being. The present study examines which diabetes information sources PWT1D use and whether specific sources are associated with improved glycemia and lower diabetes distress and anxiety. We also test whether patient engagement mediates any observed relationships between information sources and outcomes.

Methods

Study Design

This is a cross-sectional study with convenience sampling. Participants were recruited via social media platforms, via the Juvenile Diabetes Research Foundation (recently renamed Breakthrough T1D), and advertisements at local health care facilities in [area redacted due to blinding)]. Interested persons (N = 560) completed a screening questionnaire. Those who met the study criteria of being at least 18 years old, living in the United States, and using a Medtronic or Dexcom CGM as part of their T1D treatment (N = 120) were invited to participate in the full study, which involved (1) submitting the 3 months of CGM data and (2) completing a series of self-report measures. Participants were excluded from the study if the file they uploaded was not CGM data (*N*= 8), they skipped more than half of the questions in the self-report (*N* = 4) or gave the same answer to 10 or more Likert type questions in a row (*N* = 4). A total of 107 participants completed both tasks and passed these data validation checks. The study was approved by the [masked] Institutional Review Board. Of the 107, submitted CGM reports, though only 79 were usable for our CGM outcomes because the Medtronic reports only provided a handful of readings (instead of every 5 minutes).

Key Variables

Resource use was measured with a simple checklist. Participants were presented with a list of 24 resources and asked to indicate which they used. These resources included medical providers (endocrinologists, nurse practitioners, general practitioners), social media (Instagram, Facebook, YouTube, TikTok, Twitter), structured content (books, podcasts, websites), organizations (JDRF, Beyond Type 1), friends and family (family, romantic partners, friends, roommates) and other (see Table 7).

Diabetes Distress is the degree to which PWT1D struggle to adjust psychologically to the challenges of having and managing T1D (Polonsky et al., 2005). It predicts outcomes

independently of depression (Dennick et al., 2017; Skinner et al., 2020). To measure this construct, we used the Diabetes Distress Scale (Skinner et al., 2020), which is a composite of 17 items, each of which is measured on a scale from 1 (Not a problem) to 6 (A very serious problem). In our sample, these items showed good internal consistency (α= .88, ω_h = .75). Responses to this scale were averaged across participants (M = 2.16, SD = 0.27, Range 1.06-4.82) before being standardized for these analyses.

Anxiety was measured using the Patient Reported Outcomes Measurement Information System (PROMIS) Anxiety Scale (Schalet et al., 2016) which is s composite of 4 items each of which is measured on a scale from 1 (Always) to 5 (Never). In our sample, these items showed good internal consistency (α= .89, ω_h = .85). Responses to this scale were averaged across participants (M = 2.03, SD = 0.81, Range 1-4) before being standardized for these analyses.

Blood Glucose Composite Measures were calculated using CGM data. While 107 people uploaded CGM reports, those who uploaded reports from Medtronic CGM devices only included calibration glucose values and therefore did not provide the continuous measurements needed for these calculations. We ultimately used only CGM reports from Dexcom devices. Thus, we only have these measures for 79 participants in the study.

Estimated A1c

Using an algorithm minute by minute CGM data is used to estimate HbA1c. This estimate accounts for known rates of discrepancy between the CGM and HbA1c based on clinical trials.

Blood Glucose Standard Deviation

This value is the average deviation that BG values fluctuate from the mean. The clinical cut-off is 50mg/dl as an indicator of "well-managed" diabetes.

Time in Range

Time in range is highly correlated with HbA1c, and is in fact replacing it in many care settings (Beck, 2024). It is the percentage of time that a CGM measures BG between the established low BG cutoff and the high cutoff. While, this can be adjusted person to person, typically this range encompasses 80mg/dl-180mg/dl.

Patient Engagement was measured using the Consumer Health Activation Index (Wolf et al., 2018). It has been minimally applied to diabetes in previous studies (Radhika Nair et al., 2022), but we chose to use it to capture engagement with health information because it is among the strongest validated scales currently developed with the intention of capturing engagement with health information that goes beyond exposure and moves to action and implementation (Eysenbach, 2000; Wolf et al., 2018). Among its benefits is its accessibility to people of varying health literacy levels in both research and health care contexts. This scale includes 10 items rated on a scale from 1 (Strongly Agree) to 6 (Strongly Disagree). In our sample, these items showed good internal consistency (α= .85, ω_h = .66) Responses to this scale were averaged across participants (M = 2.21, SD = 0.63, Range 1.10-3.70) before being standardized for these analyses.

Statistical Analyses

We first report the rates at which participants indicate using each resource. Then, to examine whether these resources provided any benefit to PWT1D, we tested whether participants who reported using a resource experienced better outcomes – diabetes distress, time in range,

estimated A1C, blood glucose variability (SD)– controlling for participant age and years living with diabetes.

Finally, to examine the potential role of patient engagement as a link between resources and diabetes outcomes, we conducted mediation analyses in which we estimated the indirect effect of each resource on each outcome through patient engagement. We ran these mediation models for each of the 25 resources with and without years with diabetes and age included as controls in the models. We performed bootstrapping to account for uneven group sizes between those who did and did not use each resource.

Results

The average time in range in our sample was 76%. Average BG standard deviation (BGSD) was 47 mg/dl with 58% of participants averaging a BGSD below 50mg/dl and 63% of participants had an estimated A1C at the clinical goal of below 7% (which is roughly 40% more people than the national average) (CDC, 2024).

First, we examined the resources used by participants. Unsurprisingly, endocrinologists were the most frequently reported source of diabetes-related information, with nearly every participant reporting use of this resource (95%). The next most used resources were other PWT1D at 80% and Diabetes Care and Education Specialists at 74%. See Table 10 for the use frequency of each resource. We found that almost every person in our sample had a unique combination of resources that they used (see figure 10). Friends without diabetes and roommates were reported the least. Forty or more people reported getting information from nurse practitioners, podcasts, Instagram, Facebook, Google, JDRF, Beyond Type 1, Websites, and Books.

Table 10: Resource Usage Summary

Resources	N	% yes
Endocrinologist	102	95.33%
Educator	80	74.77%
Nurse Practitioner	50	46.73%
General Physician	26	24.30%
Nurse	11	10.28%
Physician's Assistant	21	19.63%
Podcast	43	40.19%
Instagram	46	42.99%
Facebook	52	48.60%
TikTok	10	9.35%
Twitter	7	6.54%
YouTube	36	33.64%
Google	64	59.81%
Roommate	2	1.87%
Friends with no diabetes	4	3.74%
Family you live with	26	24.30%
Family you do not live with	16	14.95%
Romantic partner	10	9.35%
People with T1D	86	80.37%
JDRF	48	44.86%
BeyondType1	47	43.93%
Other non-profits	30	28.04%

Resources	N	% yes
Websites	56	52.34%
Books	44	41.12%
Other	13	12.15%

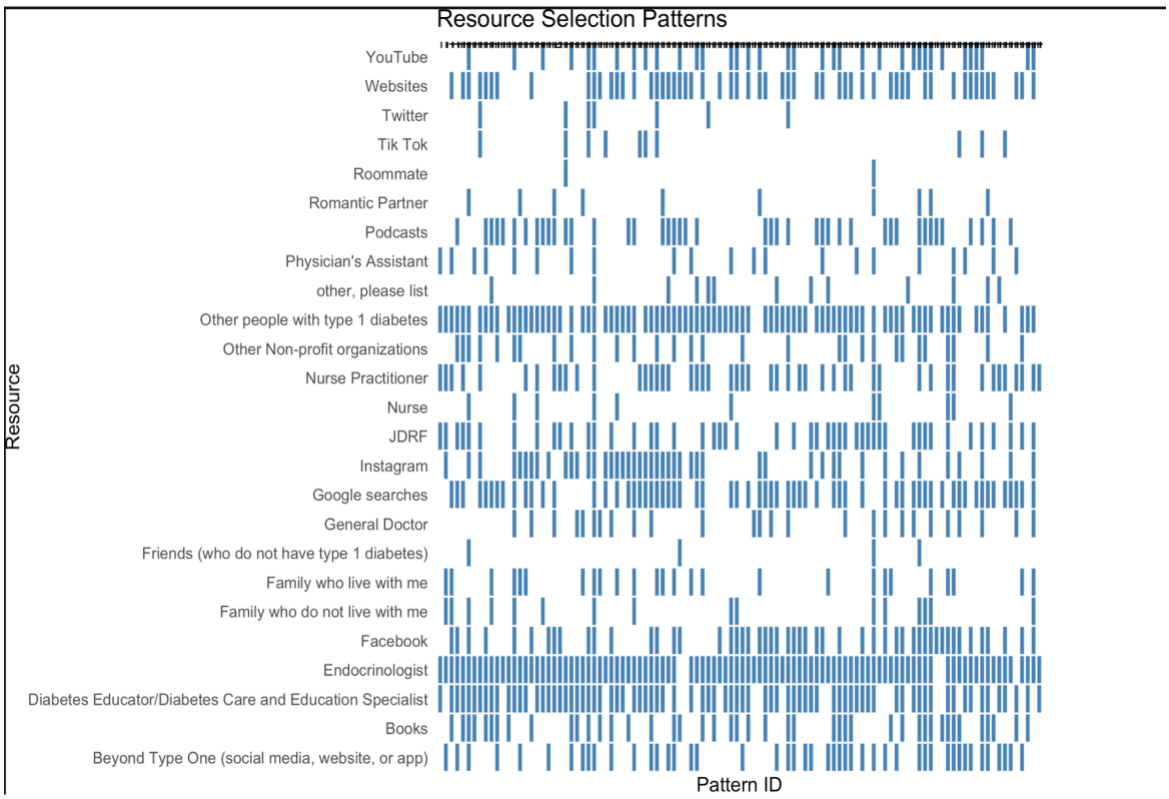


Figure 15: Patterns of resource selection are pictured with each blue line indicating that a person uses that resource. Looking across from left to right we see what combinations of resources each person uses. The denser the lines are vertically, the more frequently a resource was reported. The fact that there are no consistent horizontal lines across indicates that there are no patterns in combinations of resources used.

Next, we assessed whether the use of any of these resources was significantly associated with health outcomes (Diabetes Distress, Estimated HbA1c, standard deviation, time in range, and anxiety), controlling for participant age and years living with diabetes.

In the models that we controlled for age and years with diabetes there were significant direct effects on diabetes distress. People who reported using Instagram and Google had higher diabetes distress and those who got information from an Endocrinologist had lower diabetes distress. Reported use of podcasts and Beyond Type 1 had the same significant effects all of which indicate improvement in blood glucose levels: higher in TIR, lower estimated A1c, and lower BGSD. The use of Facebook had a significant direct effect with decreased BGSD. There was another aligned significant effect among people who reported using Google, those using Facebook, and those using TikTok with a significant increase in mean anxiety score. There was a significant decrease in mean anxiety score for people who reported getting diabetes information from a roommate. See Table 11 for the full results table.

There were no indirect effects of the Consumer Health Activation Index. 80% of our sample reported the resources they used made them feel like part of a community. The other resources that multiple participants listed that were not included in our list were Reddit (4 people), scientific/medical journals (2), and Risely health (a diabetes health coaching business) (2). Two people also mentioned learning about diabetes through their degrees, and there were individual entries for diabetes camp, experience, and learning through an antecedent child's diagnosis.

Participants reported using between two and twenty resources with a mean across all 107 participants of 8.7. Therefore, no one in our sample was only using information from their medical team.

Table 11: Full Regression Results

	Diabetes Distress		Estimated A1C		SD		TIR		Anxiety	
Resource	Indirect	Direct	Indirect	Direct	Indirect	Direct	Indirect	Direct	Indirect	Direct
Endocrinologist	-0.00	-0.04	0.00	0.00	0.00	0.00	-0.00	-0.00	0.00	0.02
	(0.00)	(0.02)	(0.00)	(0.03)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.03)

Diabetes Educator	-0.00	(0.00)	-0.04	(0.05)	0.00	(0.01)	0.02	(0.06)	0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	0.00	(0.01)	0.01	(0.07)	0.05
Nurse Practitioner	0.00	(0.01)	-0.04	(0.05)	0.01	(0.01)	0.04	(0.08)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	-0.00	(0.01)	0.01	(0.08)	0.04
General Doctor	-0.00	(0.00)	-0.07	(0.04)	-0.00	(0.01)	-0.02	(0.06)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	-0.10
Nurse	0.00	(0.00)	0.03	(0.03)	0.00	(0.00)	0.03	(0.03)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.04)	-0.02
Physician's Assistant	0.00	(0.00)	0.02	(0.04)	0.00	(0.00)	0.07	(0.06)	0.00	(0.00)	0.01	(0.00)	-0.00	(0.00)	-0.00	(0.00)	-0.00	(0.05)	-0.05
Podcasts	0.00	(0.00)	-0.00	(0.05)	-0.00	(0.02)	**-0.27**	**(0.06)**	0.00	(0.00)	**-0.01**	(0.00)	-0.00	(0.00)	**0.01**	(0.00)	0.00	(0.08)	-0.03
Instagram	-0.01	(0.01)	**0.11**	**(0.05)**	-0.00	(0.01)	0.07	(0.07)	-0.00	(0.00)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.01)	-0.00	(0.07)	0.03
Facebook	0.00	(0.00)	0.05	(0.05)	-0.02	(0.01)	**-0.14**	**(0.06)**	-0.00	(0.00)	**-0.01**	**(0.00)**	**0.00**	(0.00)	0.01	(0.00)	0.00	**(0.07)**	**0.16**
TikTok	-0.00	(0.00)	0.04	(0.03)	-0.00	(0.00)	0.06	(0.05)	-0.00	(0.00)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	-0.00	**(0.04)**	**0.07**
Twitter	0.00	(0.00)	0.00	(0.03)	-0.00	(0.00)	0.04	(0.04)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	0.00	(0.02)	0.00
YouTube	0.00	(0.00)	0.07	(0.05)	0.00	(0.01)	0.04	(0.07)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	0.00	(0.01)	0.12
Google searches	-0.00	(0.00)	**0.10**	**(0.05)**	-0.00	(0.01)	0.02	(0.07)	-0.00	(0.00)	0.00	(0.01)	0.00	(0.00)	0.00	(0.01)	-0.01	**(0.07)**	**0.19**
Roommate	0.00	(0.00)	0.01	(0.01)	-0.00	(0.00)	-0.01	(0.01)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	0.00	(0.00)	0.00	**(0.01)**	**-0.01**
Friends who do not have T1D	-0.00	(0.00)	0.02	(0.02)	0.00	(0.00)	-0.02	(0.02)	0.00	(0.00)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	0.00	(0.04)	0.01
Family (live-in)	0.00	(0.00)	-0.07	(0.05)	0.01	(0.01)	0.04	(0.07)	0.00	(0.00)	0.01	(0.00)	-0.00	(0.00)	-0.00	(0.01)	0.01	(0.06)	-0.03
Family (outside home)	-0.00	(0.00)	-0.04	(0.03)	-0.00	(0.00)	-0.07	(0.05)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	0.00	(0.00)	0.00	(0.06)	-0.01
Romantic Partner	-0.00	(0.00)	-0.01	(0.04)	0.00	(0.00)	-0.00	(0.03)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	-0.00	(0.05)	-0.06
Other people with T1D	-0.00	(0.00)	0.02	(0.05)	0.00	(0.00)	0.01	(0.06)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	-0.00	(0.00)	-0.00	(0.05)	0.07
JDRF	-0.00	(0.00)	0.06	(0.06)	0.00	(0.01)	0.08	(0.08)	0.00	(0.00)	0.01	(0.00)	-0.00	(0.00)	-0.00	(0.00)	-0.00	(0.08)	0.05
Beyond Type One	-0.00	(0.00)	0.00	(0.06)	-0.01	(0.01)	**-0.18**	**(0.07)**	-0.00	(0.00)	**-0.01**	(0.00)	0.00	**(0.00)**	**0.01**	(0.01)	-0.01	(0.08)	0.13
Other Non-profit organizations	-0.00	(0.00)	0.01	(0.05)	-0.00	(0.01)	0.05	(0.06)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	-0.00	(0.00)	-0.00	(0.08)	0.04
Websites	-0.00	(0.00)	-0.00	(0.05)	0.00	(0.00)	0.03	(0.08)	-0.00	(0.00)	-0.00	(0.01)	-0.00	(0.00)	-0.00	(0.00)	-0.00	(0.08)	-0.01
Books	-0.00	(0.00)	0.06	(0.05)	-0.00	(0.00)	0.03	(0.07)	-0.00	(0.00)	0.00	(0.01)	0.00	(0.00)	-0.00	(0.00)	0.00	(0.09)	-0.02

	Diabetes Distress				Estimated A1C				SD				TIR				Anxiety		
Resource	Indire ct		Dire ct		Indire ct		Dire ct		Indire ct		Dire ct		Indire ct		Dire ct		Indire ct		Dire
Endocrinologist	-0.00	(0.00)	-0.04	(0.02)	0.00	(0.00)	0.00	(0.03)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.03)	0.02
Diabetes Educator	-0.00	(0.00)	-0.04	(0.05)	0.00	(0.01)	0.02	(0.06)	0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	0.00	(0.01)	0.01	(0.07)	0.05
Nurse Practitioner	0.00	(0.01)	-0.04	(0.05)	0.01	(0.01)	0.04	(0.08)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	-0.00	(0.01)	0.01	(0.08)	0.04
General Doctor	-0.00	(0.00)	-0.07	(0.04)	-0.00	(0.01)	-0.02	(0.06)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	-0.10
Nurse	0.00	(0.00)	0.03	(0.03)	0.00	(0.00)	0.03	(0.03)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.04)	-0.02
Physician's Assistant	0.00	(0.00)	0.02	(0.04)	0.00	(0.00)	0.07	(0.06)	0.00	(0.00)	0.01	(0.00)	-0.00	(0.00)	-0.00	(0.00)	-0.00	(0.05)	-0.05
Podcasts	0.00	(0.00)	-0.00	(0.05)	-0.00	(0.02)	**-0.27**	**(0.06)**	0.00	(0.00)	**-0.01**	(0.00)	-0.00	(0.00)	**0.01**	(0.00)	0.00	(0.08)	-0.03
Instagram	-0.01	(0.01)	**0.11**	**(0.05)**	-0.00	(0.01)	0.07	(0.07)	-0.00	(0.00)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.01)	-0.00	(0.07)	0.03
Facebook	0.00	(0.00)	0.05	(0.05)	-0.02	(0.01)	**-0.14**	**(0.06)**	-0.00	(0.00)	**-0.01**	**(0.00)**	**0.00**	(0.00)	0.01	(0.00)	0.00	**(0.07)**	**0.16**
TikTok	-0.00	(0.00)	0.04	(0.03)	-0.00	(0.00)	0.06	(0.05)	-0.00	(0.00)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	-0.00	**(0.04)**	**0.07**
Twitter	0.00	(0.00)	0.00	(0.03)	-0.00	(0.00)	0.04	(0.04)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	0.00	(0.02)	0.00
YouTube	0.00	(0.00)	0.07	(0.05)	0.00	(0.01)	0.04	(0.07)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	0.00	(0.01)	0.12
Google searches	-0.00	(0.00)	**0.10**	**(0.05)**	-0.00	(0.01)	0.02	(0.07)	-0.00	(0.00)	0.00	(0.01)	0.00	(0.00)	0.00	(0.00)	-0.01	**(0.07)**	**0.19**
Roommate	0.00	(0.00)	0.01	(0.01)	-0.00	(0.00)	-0.01	(0.01)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	0.00	(0.00)	0.00	**(0.01)**	**-0.01**
Friends who do not have T1D	-0.00	(0.00)	0.02	(0.02)	0.00	(0.00)	-0.02	(0.02)	0.00	(0.00)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	0.00	(0.04)	0.01
Family (live-in)	0.00	(0.00)	-0.07	(0.05)	0.01	(0.01)	0.04	(0.07)	0.00	(0.00)	0.01	(0.00)	-0.00	(0.00)	-0.00	(0.01)	0.01	(0.06)	-0.03
Family (outside home)	-0.00	(0.00)	-0.04	(0.03)	-0.00	(0.00)	-0.07	(0.05)	-0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	0.00	(0.00)	0.00	(0.06)	-0.01
Romantic Partner	-0.00	(0.00)	-0.01	(0.04)	0.00	(0.00)	-0.00	(0.03)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	0.00	(0.00)	-0.00	(0.05)	-0.06
Other people with T1D	-0.00	(0.00)	0.02	(0.05)	0.00	(0.00)	0.01	(0.06)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	-0.00	(0.00)	-0.00	(0.05)	0.07
JDRF	-0.00	(0.00)	0.06	(0.06)	0.00	(0.01)	0.08	(0.08)	0.00	(0.00)	0.01	(0.00)	-0.00	(0.00)	-0.00	(0.00)	-0.00	(0.08)	0.05
Beyond Type One	-0.00	(0.00)	0.00	(0.06)	-0.01	(0.01)	**-0.18**	**(0.07)**	-0.00	(0.00)	**-0.01**	(0.00)	0.00	**(0.00)**	**0.01**	(0.01)	-0.01	(0.08)	0.13
Other Non-profit organizations	-0.00	(0.00)	0.01	(0.05)	-0.00	(0.01)	0.05	(0.06)	0.00	(0.00)	0.00	(0.00)	-0.00	(0.00)	-0.00	(0.00)	-0.00	(0.08)	0.04
Websites	-0.00	(0.00)	-0.00	(0.05)	0.00	(0.00)	0.03	(0.08)	-0.00	(0.00)	-0.00	(0.01)	-0.00	(0.00)	-0.00	(0.00)	-0.00	(0.08)	-0.01
Books	-0.00	(0.00)	0.06	(0.05)	-0.00	(0.00)	0.03	(0.07)	-0.00	(0.00)	0.00	(0.01)	0.00	(0.00)	-0.00	(0.00)	0.00	(0.09)	-0.02

Discussion

Our results indicate that every PWT1D has a unique pattern of resource use reflective of the intense need and multi-faceted process of obtaining desperately needed information. Engagement with podcasts, Facebook and Beyond Type 1 is directly associated with improved diabetes management outcomes while Google and TikTok are associated with higher anxiety. Our cross-sectional analysis does not allow us to make causal claims about why outcome values are different between resource-use groups, but increases in anxiety among people using a resource makes sense because in some cases anxiety drives a person to seek information, and an onslaught of information (such as that from a Google search) can also create anxiety. This study did not allow for the assessment of causal relationships and thus there is a strong need for future studies that do so. The lower anxiety levels among people who get information from their roommates makes sense in the context that some of the anxiety-producing aspects of the disease (e.g., the fear of slipping into a low blood sugar and dying in the middle of the night) is alleviated by living with someone who engages with diabetes information.

Despite the goal of capturing engagement with health, it seems likely that the CHAI did not capture the engagement taking place in this community. Based on the literature and corroborative finding that people use online resources in addition to their medical care, it is possible that part of the reason that we did not pick up on any mediating effects is that the engagement that CHAI captures is too directly related to the medical protocol (Gabarron et al., 2020) and does not capture engagement with additional information outside of that which is provided by the medical community. Further research needs to be conducted that focuses on how to capture the uptake and implementation of information among the community of PWT1D. The CHAI did not pick up on any significant engagement and yet we know that people are engaging with the information.

Limitations

1) Based on their CGM data the group of PWT1D that we reached have a substantially higher success reaching glycemic goals than the general population and so our sample represents a sub-group that is especially successful in their diabetes management strategies.
2) There is no one in our sample that is not using additional resources outside of their medical team. It is possible that this is because most people with T1D seek external information sources, but could also be a reflection of our recruitment strategy.
3) We primarily recruited from social media and so many of our participants were part of the Diabetes Online Community (DOC). We did have flyers in a couple clinics but very few people found the study through clinic flyers. This sampling bias likely means that there are stronger impacts of resource-use that we could not pick up on because our entire sample was using additional resources.
4) We were not able to compare people who use additional resources to people who only use information from their medical team. We were however, able to compare people who use each resource to people who do not, and to describe 107 people who live with diabetes in the US who are extremely engaged with their diabetes.

Future research that recruits directly from clinics and doctor's offices is needed in order to capture perspectives from more PWT1D who are not connected to the DOC or in person community, and to ascertain whether there any people with T1D who do not use outside resources.

A diabetes-specific construct for engaging with information needs to be explored. One immediate way forward that we suggest, is medical protocol that works in concert with outside

informational resources like social media, podcasts and local support groups. There is some literature assessing this area (Gabarron et al., 2020; Grosberg et al., 2016) and there have been some successful trial interventions directed on this type of partnership/encouragement (Petrovski & Zivkovic, 2017).

Conclusions

This sample of people with T1D are using many resources to gather information about disease management (Mean = 5). Google, Facebook, Podcasts, Instagram, roommates, and other people with T1D are the only resources that indicated differences in outcomes. Nearly everyone used information from their endocrinologist and so this was not a resource that we were able to compare use and non-use of. The measure of patient engagement did not pick up on any moderating effect for any of the resources indicating a strong need for a better instrument to engagement health information engagement among PWT1D.

Bridge to Chapter V

This chapter illustrated the power of the expert patient in driving the T1D community into a better future. We found that PWT1D use a large number of resources to supplement the information they receive from their doctor and cater their care to their specific needs. Based on our findings there is a strong need to a better validated scale to capture patient engagement with health information resources. A theme throughout this dissertation is areas where there is a strong need for future research on diabetes, in order to move the findings documented here forward. The next chapter will summarize what each study found and highlight common features like this need for future interventions.

CHAPTER V: CONCLUSIONS AND FUTURE DIRECTIONS

This dissertation examined nuanced and multidimensional aspects of diabetes on cellular, population, and intra-individual scales. Shifting away from the assumption that the low rates of diabetes treatment success are due to patient failure, this work considered biological factors and care models to determine whether there are gaps in diabetes treatment and monitoring. Chapters II and III provided evidence that the relationship between diabetes (determined based on diagnosis and/or elevated HbA1c) and inflammation (measured through CRP) are deeply intertwined, but not as clear cut as we hypothesized. While the approach in chapter III enables capturing added levels of complexity, this relationship requires further study. In chapter IV, I focus on the use of resources among PWT1D and assess whether any groups who use one of the of 23 resources have different averages in outcome levels. The following provides a brief summary of the research presented in this dissertation along with a brief discussion on implications and future directions.

Research objectives

There were two main research objectives in this work: 1) to enhance characterization of inflammation and diabetes and 2) to capture resource use and its effects among people living with type 1 diabetes. There were additional objectives within each of these main objectives, such as the characterization of diabetes and inflammation in each of the two countries (China and Mexico) in which these relationships were examined. It is also worth noting that while chapter II was initially designed to test ideas related to diabetes, the data were not able support the complex models initially designed. Consequently, the models presented here treat all chronic disease equally and assess the relationship between multimorbidity and chronic inflammation. It is

remarkable that diabetes stands out in its correlation to inflammation even when the model is not explicitly focused on it.

Data Collection Methods

The data in the first two chapters of this dissertation was collected as part of the World Health Organization Wave 1 from of The Study on global AGEing and adult health (SAGE) collected in 2007-2010. This data included in-person surveys as well as HbA1c and CRP measures in a subsample. The data in the third chapter was collected through an online study in the US that included uploading reports from continuous glucose monitors, an online survey containing validated scales as well as researcher generated questions, and a subset of interviews conducted between 2023 and 2025.

Hypotheses

The research presented here tested the following six hypotheses.

1) Despite at target HbA1c < 6.5%, people diagnosed with diabetes have higher CRP on average than people who do not have diabetes.

2) We will see a flattening of the slope indicating the relationship between CRP and HbA1c among people who have diabetes since people who have diabetes and lower HbA1c will still have relatively elevated CRP.

3) We will see the same patterns in both countries, with higher CRP correlating to HbA1c continuously across all statuses of diabetes (from no diabetes to diabetes not meeting treatment goals)

4) a demonstration of an approach for studying multi-dimensional, complex, physiological processes tied to disease development and progression with a special interest in what this might reveal about diabetes, multimorbidity, and chronic inflammation will in fact reveal novel findings

5) Some diabetes information sources people with T1D (PWT1D) use are associated with improved glycemia and lower diabetes distress and anxiety.

6) Patient engagement mediates any observed relationships between information sources and outcomes

Summary of main findings

In chapter II although we did find important connections between diabetes and inflammation, it was only true that despite at target HbA1c < 6.5%, people diagnosed with diabetes had higher CRP on average than people who do not have diabetes in China. Thus, our hypothesis that we would see the same trends in both countries was also not supported. There were nuances in the Mexico data that support the likely explanation that the underlying physiology is the same, but factors beyond what we measured are likely causing different trends. The main observed anomaly is that people with prediabetes have significantly higher CRP levels than people who have diabetes.

In chapter III we found that even when we treated all chronic diseases as equal in a study of multimorbidity and inflammation, diabetes stood out as particularly connected to inflammation. We found that diabetes plus any other chronic disease characterized the highest inflammation groups in both countries. This observation of patterning was only possible using our extension of the novel statistical method (MAIHDA). Thus, it is a strong demonstration of an

approach for studying multi-dimensional, complex, physiological processes tied to disease development and progression. This particular application to multimorbid chronic disease revealed novel findings about patterning among diabetes, multimorbidity, and chronic inflammation; namely that people with diabetes in combination with any other chronic disease regardless of whether it was arthritis, pulmonary issues, or hypertension, have the highest average CRP compared to other combinations of those diseases.

In chapter IV we found that some information sources people with T1D (PWT1D) use are associated with improved glycemia and lower diabetes distress. However, an increase in anxiety was correlated with the use of Google and Instagram. While we know that there must be some sort of mediation involved in gleaning information from a resource and consequent changes in health outcomes, out moderation did not pick up on any effect. We hypothesize that this is because the particular engagement between PWT1D and informal sources of information is not captured by the validated scale that we used (the Consumer Health Activation Index), and in fact there is no validated scale that currently exists that captures this type of resource engagement.

Theoretical Approaches

Black Feminism Theory

Black feminism and crip theory collectively allow for the human component of diabetes to remain a high priority in this work. While the biology poses fascinating puzzles that are interesting to examine at the cellular level, the goal of the work presented here is to relieve human suffering caused by diabetes. As mentioned in the introduction, Audre Lorde writes of the need to "define and empower" rather than divide and conquer, and this is the perfect framing for understanding the relationship between T1D and T2D. Both medically and socially, the two

types need to be clearly defined based on their differences, but their similarities need to be embraced as well. The physiological similarities allow us to better understand the disease when we look at them together. The social similarities of stigma and misunderstanding are best fought as a united community, though currently the T1D community is quick to explain the T2D is the "stigmatized one" and the autoimmune one is the one that deserves compassion.

Biocultural Theory

Biocultural anthropology enables the simultaneous study of daily experiences and cellular biology. The work presented here demonstrates that the two are intricately connected and often the complexity of daily life creates physiological changes that deviate from the expected patterns were biology to exist in a vacuum. The combination of methods used in the research this dissertation reports reflect the biocultural framework as it allows for the entanglement of quantitative and qualitative research methods. Though the interviews done as part of T1DES are not directly reported on here, the insights provided by participants had a profound impact on this author and have contributed to the sharpening of my ability to define and interrogate diabetes. Lastly, the biocultural approach frames the very defining of disease as a component of culture. I use a critical lens of the definition of conceptualization of the very idea of diabetes throughout the work presented here.

Implications

This research allows us to better understand the human experience of diabetes, but also demonstrates that there may be future opportunities to lessen the global burden of diabetes if we continue to focus on diabetes and inflammation, and the pathways that are involved in their relationship. Treatment and monitoring focused on inflammation has the potential to shed light on the processes that lead to diabetes complications, and a better understanding of this could

potentially create a path to slowing down complications in people who have diabetes. Additionally, some research points to inflammation as a precursor to diabetes (Kato et al., 2019) and thus future examinations could help to prevent diabetes altogether.

Future Directions

Future research would benefit from study design explicitly centered on diabetes and inflammation longitudinally. Additionally, research designed with MAIHDA in mind would be able to take full advantage of the novel properties that MAIHDA models offer statistically. There also remain future publications to come from some of the data collected as part of this dissertation. Forthcoming publications include an examination of self-adjustment decisions made by people living with T1D, an evolutionary medicine informed explanation of type 1 diabetes, a characterization of blood sugar symptoms and a mapping of the physiological pathways that trigger them, and examination of current blood glucose metrics and the introduction of novel statistical methods for capturing blood glucose variability.

The resource-use of people with T1D captures a phenomenon in the T1D community that currently creates a fission between the medical community and the lived reality of life with type 1 diabetes. Documentation of how PWT1D navigate the "gap between appointments" (Jeswin et al., 2023) helps to capture the nuances required for blood sugar management and sanity for people living with T1D. Future research in this area could delve deeper into the ways that people are using resources beyond their medical team to supplement what is provided to them. Additionally, new scales that capture T1D-specific engagement with their treatment and resources that inform treatment decisions need to be developed.

Contributions to Biology

There are some aspects to this work that make it stand out that are worth noting: typically research focused on a niche population is for the benefit of that population. In this case, while the groups I am interested have highly specific qualities such as people with at target diabetes or people who have access to CGMs, the findings hold implications for all people with diabetes. The community intended to benefit from this work is much larger than the community studied. Similarly, many of the complex relationships between diabetes and inflammation surveyed here can be applied to study of other autoimmune, inflammatory diseases. The cellular, population, and experiential levels of this data offer a wholistic understanding of diabetes with take-aways that can be extrapolated beyond diabetes.

Concluding Statement

Diabetes is rising rapidly and creating an intense global burden emotionally, financially, and physically. The work presented here provides small-scale solutions that could expand into bigger solutions should future research be done to further the directions begun here. Inflammation is known to be associated with diabetes, but it is not currently monitored in people with T1D. By taking inflammation and disease-related informational resources (primarily those created by other people living with the disease) into closer consideration in clinical and research settings, we could begin to improve diabetes management success and consequently better the quality of life of those living with diabetes. Future inclusion of T1D in anthropological work would also help to continue to generate new ideas for interventions and treatment approaches. It is this author's hope that this research is the first step in bringing T1D into anthropological awareness, and increasing awareness of the relevance of inflammation to the study and treatment of both type 1 and type 2 diabetes.

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